The synthesis of heterocyclic compounds related to natural products.

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The Synthesis of Heterocyclic Compounds

Related to Natural Products

By

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Declaration

This work has not been previously accepted in substance for any degree and is not being concurrently submitted in candidature for any other degree.

This thesis is the result of my own investigations undertaken at the University of Wales Swansea during the period of November 1993 and November 1996. Other sources are acknowledged in references.

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Summary

Chapter 1 deals with an introduction to hypervalent iodine reagents and their recent uses as phenolic oxidation reagents to give a number of heterocyclic compounds. The mechanism of the reaction is also discussed.

Chapter 2 concentrates on the production of 3-substituted phenols and the subsequent hypervalent iodine oxidation to see if a variety of chromenone compounds can be formed via intramolecular nucleophilic attack. Whilst not successful in generating the desired compounds a number of oxidised products were isolated.

Chapter 3 deals with ways of making the 3-nucleophilic side chain on various phenols more rigid in the hope of aiding cyclisation. A number of ideas were explored however all were unsuccessful, in that again the desired compounds were not obtained. One reaction of note from this chapter was that the epoxide ring used to give rigidity to the nucleophilic side chain, withstood the PIDA oxidation despite the presence of acid.

Chapter 4 takes the idea in chapter 3 one step further and deals with epoxides as the group utilised to bring rigidity to the nucleophilic side chain. All products, bar one, proved successful in generating their appropriate epoxychromanones, and that which didn't provided an alternative cyclised product.

The final brief chapter deals with possible future work now that some success has been achieved and suggests ways forward from this.

Abbreviations

The abbreviations used in this thesis are listed below:

Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
CI	Chemical ionisation
Conc	Concentrated
DMF	*N,N*-Dimethylformamide
Et	Ethyl
EI	Electron ionisation
Fig.	Figure
HPLC	High Pressure Liquid Chromatography
IR	Infra red
Mass Spec.	Mass spectrometry
MCPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MeO	Methoxyl
MeOH	Methanol
MeSOH	Methane sulphonic acid
Min	Minutes
NMR	Nuclear magnetic resonance
Pd/C	Palladium on charcoal

Ph	Phenyl
PIDA	Phenyliodonium diacetate
PIFA	Phenyliodonium *bis*(trifluoroacetae)
Ref.	Reference
TBDMS	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
UV	Ultra violet

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Chapter 1

Introduction

1.1 The role of phenolic oxidation in nature

Phenolic oxidation is a very important process in nature and occurs on a very large scale. Oxidative coupling of phenols has been recognised as playing a role in the synthesis of many biologically important natural compounds such as lignins[1], lignans[2], flavonoids[3], tannins[3], plant and insect pigments[4], several antibiotics[3] and an estimated 10% of all known alkaloids[3] .

Phenols are readily oxidised and it is therefore no surprise that phenolic oxidation has become of increasing importance to the synthetic organic chemist .

Most biosynthetic phenolic oxidations, it is agreed , proceed via one electron processes to give aryloxy radicals ($ArO^{\cdot}$), and it is these species that undergo further reaction, be it homolytic or heterolytic coupling, radical insertion, or quinone methide formation[5] .

Phenolic oxidation processes have also been induced and studied by electrochemical methods[6,7] .

1.2 Aryloxenium ions

Aryloxenium ions, (ArO^{+}), the intermediates from two electron phenolic oxidation processes, have been less well studied than the corresponding radicals, although aryloxenium ions have been implicated in biological processes[8,9] . They too have been produced via electrochemical oxidation, particularly in acid solutions. They have also been postulated as intermediates in biosynthetic phenolic oxidation and phenolic coupling reactions[10,11].

Synthetic chemists have been aided by a wide variety of oxidants in the laboratory, particularly metal containing compounds derived from Fe^{III},[12] Ag^{I},[13] Pb^{IV},[14] V^{IV}[15] etc..

Although such oxidations are short and operationally simple, they employ highly toxic oxidants to provide moderate to low yields of product mixtures and therefore a need for the development of simpler and safer organic oxidants is of undoubted synthetic interest.

Potentially, aryloxenium ions would appear to offer many advantages in synthesis over their corresponding radicals, and these were pointed out by Pelter *et al.*[16] who suggested that aryloxenium ions may be produced by various methods as shown by equations (1) - (3).

$$ArOH \longrightarrow ArOX \longrightarrow ArO^{+} + X^{-} \quad (1)$$

$$ArOH \longrightarrow ArOX^{+} \longrightarrow ArO^{+} + X \quad (2)$$

$$ArOH \longrightarrow ArOX[N] \longrightarrow ArO^{+} + X[N-2] \quad (3)$$

X would be a heteroatom capable of a ready change in valency from N to N-2.

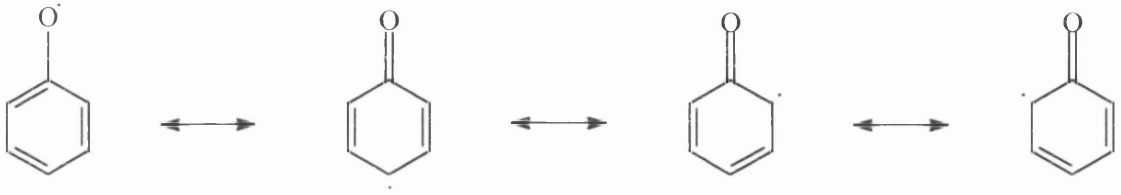
Equations (1) and (2) show the production of the aryloxenium ion as a dissociation rather than a step requiring oxidation, as the phenols are firstly transformed into intermediates ArOX with a good leaving group bonded to the oxygen, and then the nucleofugal group is eliminated to leave the oxenium ion. Equation (3) shows that accompanying dissociation, there may be a valency change in the previously attached group X.

For all three equations, if X can be attached to a particular hydroxyl group, the following reactions will be specific, regardless of whether other oxidisable groups are present. It has been pointed out in an important paper by Waters[17], that on the basis of the

expected lower electron density on the oxygen atom of aryloxenium ions, as compared with the aromatic ring in PhO· radicals, it would be sensible to predict that the radicals would dimerise by C - O - C bond formation rather than C - C bond formation.

The opposite however could be said of phenoxenium ions which calculations[18] show, are far more electron deficient in the ring than on the electronegative oxygen atoms, possibly leading to more C - C than C -O - C bond formation.

Aryloxy radicals, ArO· , can easily dimerise in many ways by combinations of many forms of the radicals shown in Scheme 1.



Scheme 1

However aryloxenium ions will not react with each other but will react with nucleophilic groups by either intra- or intermolecular processes. This allows two dissimilar units to couple, one as an aryloxenium ion and the other as a neutral molecule. If benzylic protons are available in the aryloxenium ion precursor, they may be readily lost to give quinone methides[19], ready for substitution[19], cyclisation and addition[20].

1.3 The criteria for an oxidising agent to generate aryloxenium ions

Using the above equations (1-3) as a basis for generating aryloxenium ions, ArO^+, means that the choice of X is very important.

As the natural polarisation of a phenol to give a phenoxy anion is to be reversed, then X must be an excellent leaving group.

For synthetic purposes, the following conditions should be fulfilled:-

i) ArOX should be readily accessible

ii) ArOX should decompose in mild conditions to ArO^+

iii) X^- or (X[N-2]) should not be a strong nucleophile to avoid attack on ArO^+

By taking these considerations into account, hypervalent iodine reagents such as phenyliodonium diacetate (PIDA), phenyliodonium bis-trifluoroacetate (PIFA) and Kosers' reagent, hydroxytosyloxy iodobenzene, have all been recently utilised as reagents for the oxidation of phenols.

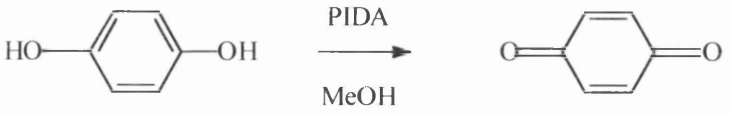
1.4 Phenyliodonium Diacetate

1.4.1 Phenyliodonium Diacetate (PIDA)

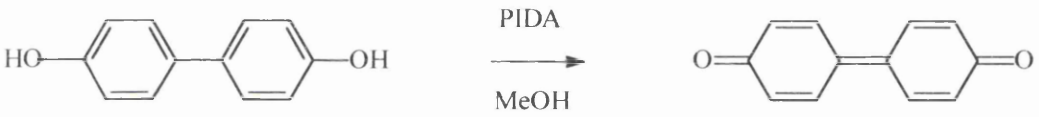
PIDA, ($PhI(OAc)_2$), has been widely utilised as a phenolic oxidation reagent and is cheap and commercially available. On reaction it yields iodobenzene, ArO^+ and AcO^-, a poorly nucleophilic anion. PIDA was first used to oxidise monohydric phenols to give low yields of the corresponding p-quinones. It was also used to substitute an acetoxy group into 4 substituted phenols when hydrogen or bromine were in the *para* position[21].

1.4.2 Oxidation of 1,2 and 1,4-quinols

Phenolic oxidation using PIDA was extended by Pelter *et al.*[22] who showed it to be an excellent oxidising agent by oxidising various 1,2- and 1,4-quinols to yield the corresponding 1,2- and 1,4-quinones in excellent yields, under very mild conditions.(eqns 4 and 5)



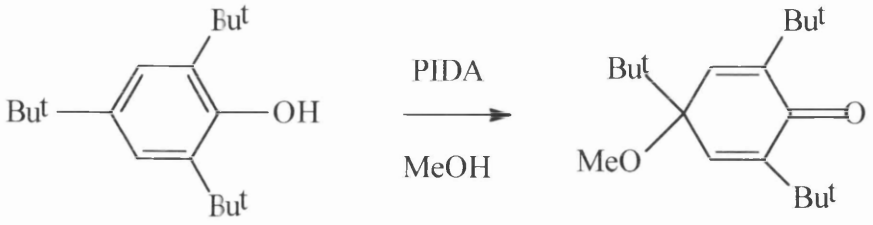
(4)



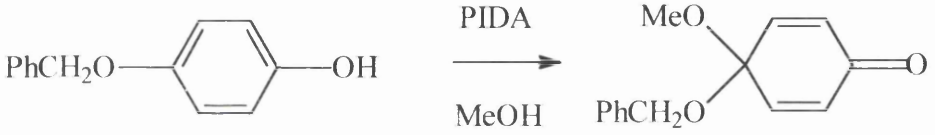
(5)

1.4.3 Oxidation of 4-alkyl and 4-alkoxyphenols

In the same work it was also shown that 4-alkyl-4-methoxycyclohexa-2,5-dienones are formed in acceptable isolated yields (eqn 6) from 4-alkylphenols. Quinone ketals (4,4-dialkoxycyclohexa-2,5-dienones) also result in excellent yields if the substituent on the phenol is an alkoxy group (eqn 7).



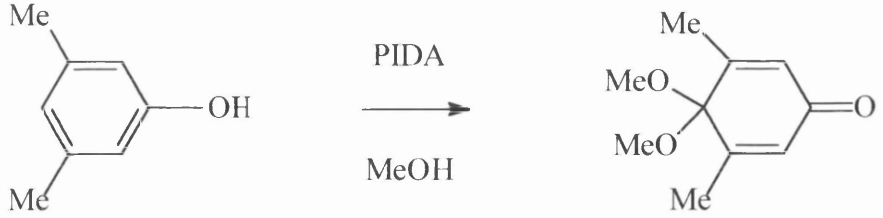
(6)



(7)

Mixed quinone ketals can also be made in this way, demonstrating how synthetically useful is this mild oxidation method (eqn 7).

It was also noted that *p*-quinone ketals were directly formed from 4- unsubstituted phenols even when this position was relatively hindered (eqn 8).

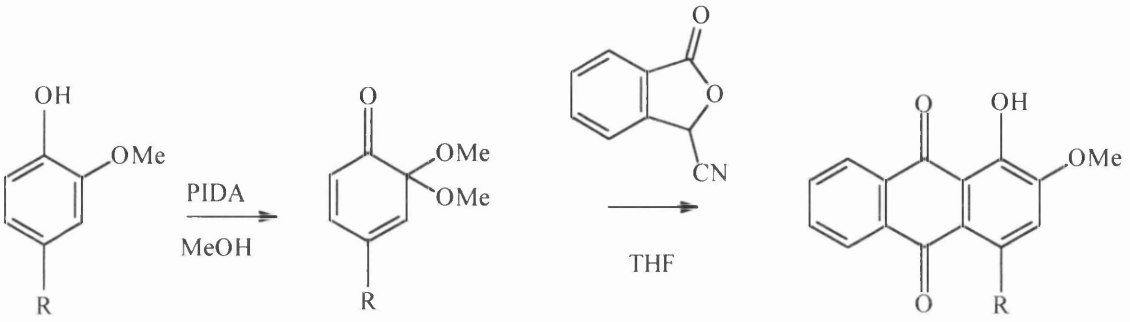


(8)

1.4.4 Oxidation of 2-substituted phenols

More recently however, 2-substitution was shown to occur when a methoxy group was attached at C-2 (Scheme 2). Substituted phenols were oxidised by PIDA in methanol to yield either cyclohexa-2,5-dienones or the isomeric 2,4-dienones depending on the structure

of the phenol. Annulation of these products with the anion of 3-cyanopthalide affords access to anthraquinones not previously accessible[23].

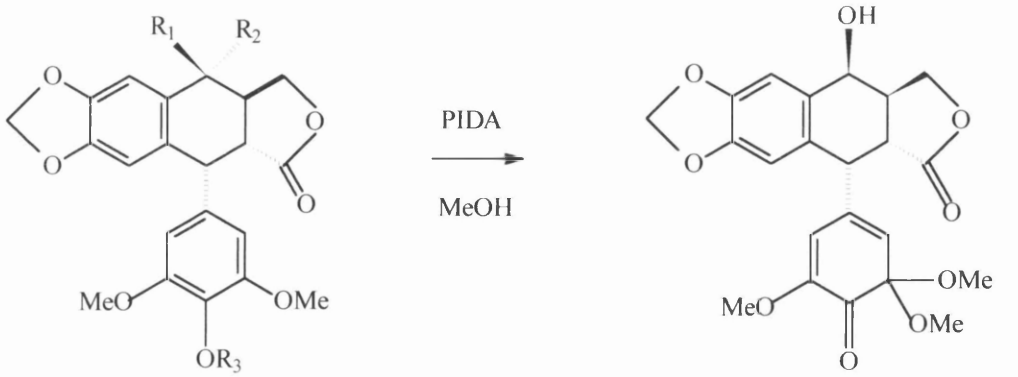


where R = allyl, Me, t-Bu

Scheme 2

ortho-Quinone monoacetals have in general attracted little attention because of their tendency to self-dimerise, although in this case a combination of rapid oxidation using PIDA and workup together with an inert by-product, iodobenzene , which can be carried through the annulation sequence, allows the reaction to proceed.

ortho-Substitution has also been observed on oxidation of a heavily substituted podophyllotoxin derivative[24] (eqn 9) also containing *ortho*-methoxy groups. The product observed from the reaction represents a totally novel modification of podophyllotoxin, derivatives of which are of interest, as many have been shown to possess anti-cancer properties.



(9)

R_1 = OH R_2 = R_3 = H

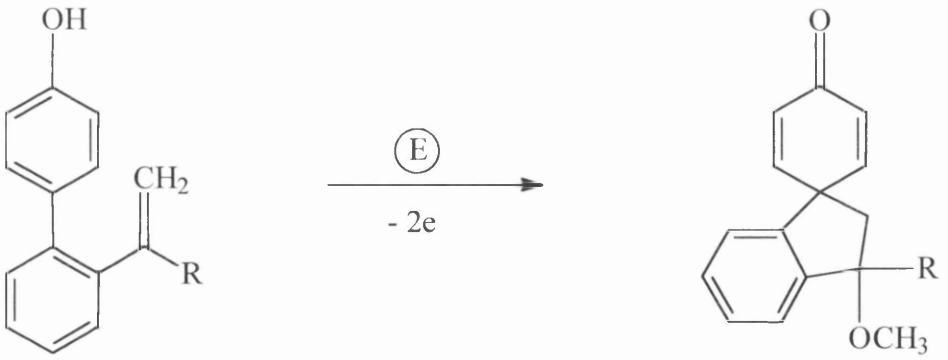
Organoiodine reagents have been utilised in the synthesis of a wide variety of natural products such as spirodienones[25,26,27] lignans[28] and anthraquinones[23] through phenolic oxidation.

1.5 The Mechanism of Hypervalent Iodine Oxidation

The exact mechanism by which hypervalent iodine oxidation occurs is not known.

Electrochemical methods have long been used to induce and study one electron oxidations but have also recently been used to study two electron phenolic oxidation processes to give aryloxenium ions, ArO^{+} [29].

Utilising coulombetry to gauge the number of electrons transferred under anodic conditions, Swenton *et al.*[30,31,32] came to the conclusion that oxidation involved a two electron transfer from the phenolic compound (Scheme 3).



1 **2**

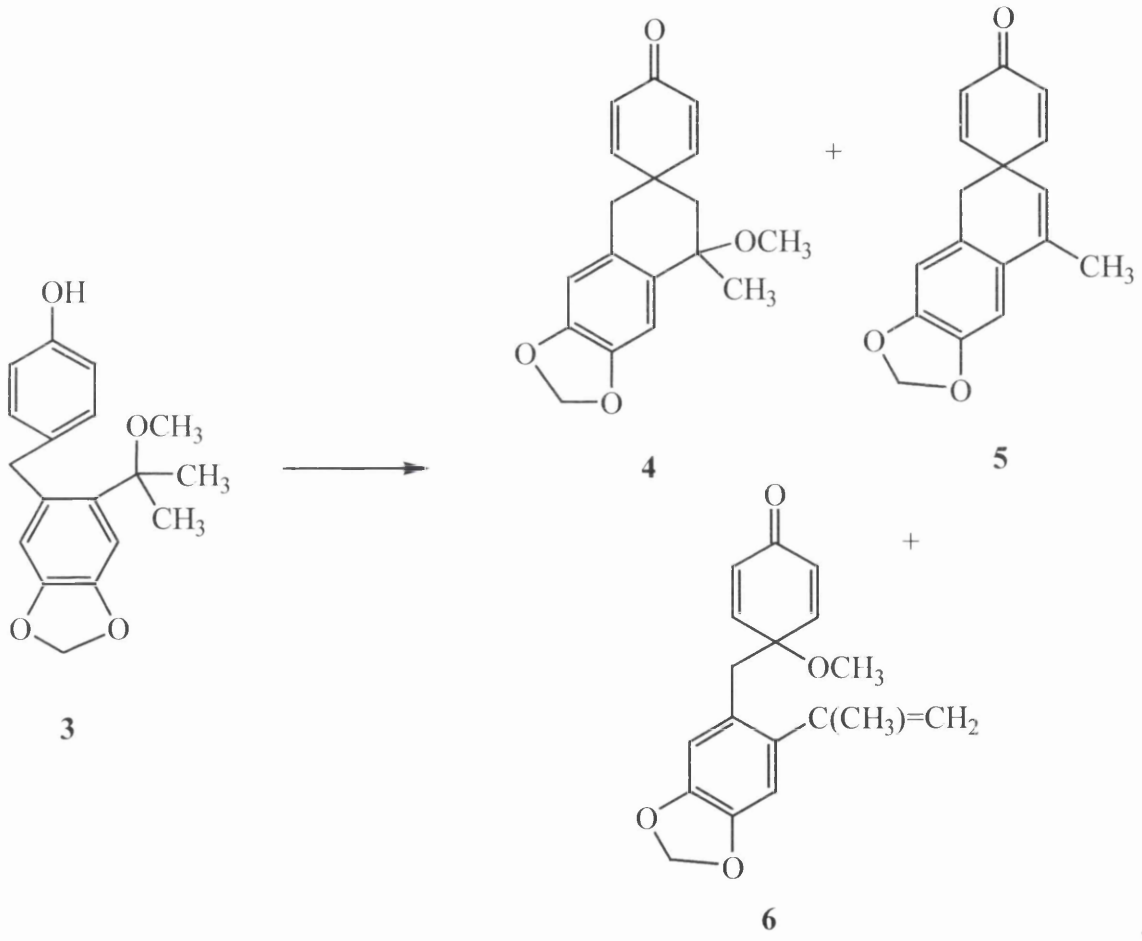
Scheme 3

They have suggested that the anodic cyclisation could be viewed in two ways, firstly, that cyclised compound (**2**), (Scheme 3), was formed by the reaction of the olefinic side

chain with a phenoxonium ion intermediate, and secondly, that it was formed by nucleophilic attack of the phenol on an oxidised styrene double bond.

Chemical oxidation using PIDA as the oxidising agent was also attempted on the *p*-substituted phenol (**3**) as it had been previously shown to be a complementary reagent for effecting the oxidative cyclisation for a number of phenolic reagents.[22]

Results showed that the phenol was selectively oxidised to give the following products (Scheme 4).



Scheme 4

When discussing the mechanism of PIDA oxidation of phenols, it has been suggested that the first step is the exchange reaction between the phenol and the hypervalent iodine

reagent.

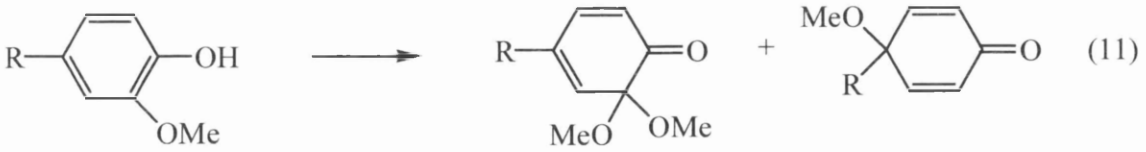
On this basis Swenton *et al.* came to the conclusion that the phenol moiety of (**1**) would be selectively oxidised in spite of the similar oxidation potentials of the phenol and styrene moieties.

The resulting mixture of products obtained above would seem to back this theory whereby cyclised products (**4** and **5**) predominate.

Following on from this it was suggested that while it is not necessarily true that the intermediate from anodic and PIDA oxidation was the same species, the reaction is best viewed 'as cyclisation of an olefinic side chain on a phenoxenium ion intermediate' .

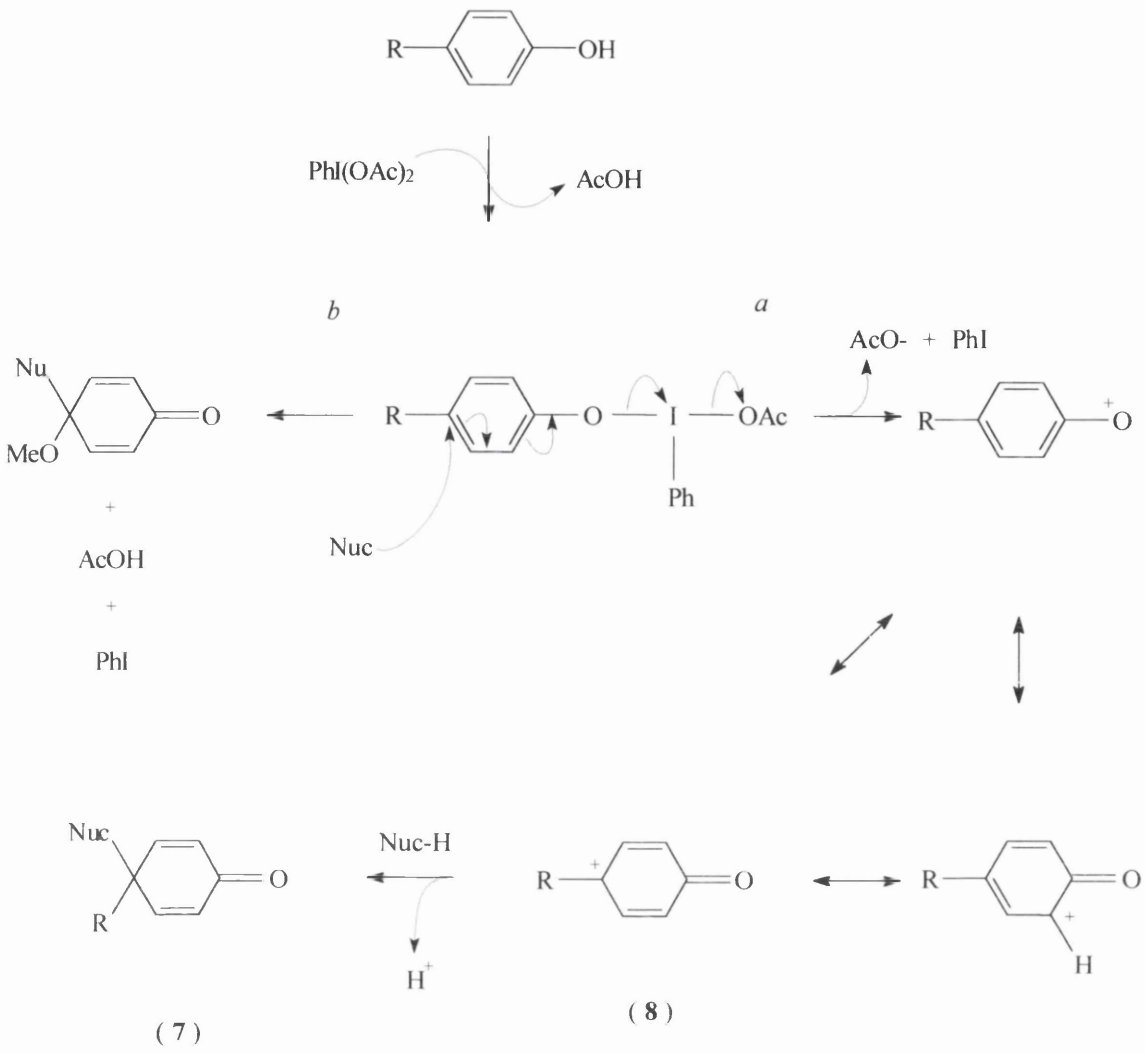
The mechanism has been more recently explored by Pelter *et al.*[33] who had earlier[22] experimented on various substituted phenols e.g. eqns 10 and 11.

(10)



(11)

They came to the conclusion that two possible pathways are responsible for the products obtained from PIDA oxidation. (Scheme 5).



Scheme 5

The products may be formed by two different pathways, routes *a* and *b* above. Route *a* involves the production of solvated phenoxenium ions which would then subsequently react with the nucleophiles present to give the observed product (**7**). Route *b* on the other hand would involve direct displacement from undissociated intermediates to give the final products (**7**). Pelter argues strongly in favour of route *a* which in association with MOPAC calculations carried out on substituted phenoxenium ions, give evidence of favourable electron distribution at the point of attack by nucleophiles.[18] Thus when the phenol has a C-2 substituent such as an alkoxy group which is capable of stabilising a positive charge, then

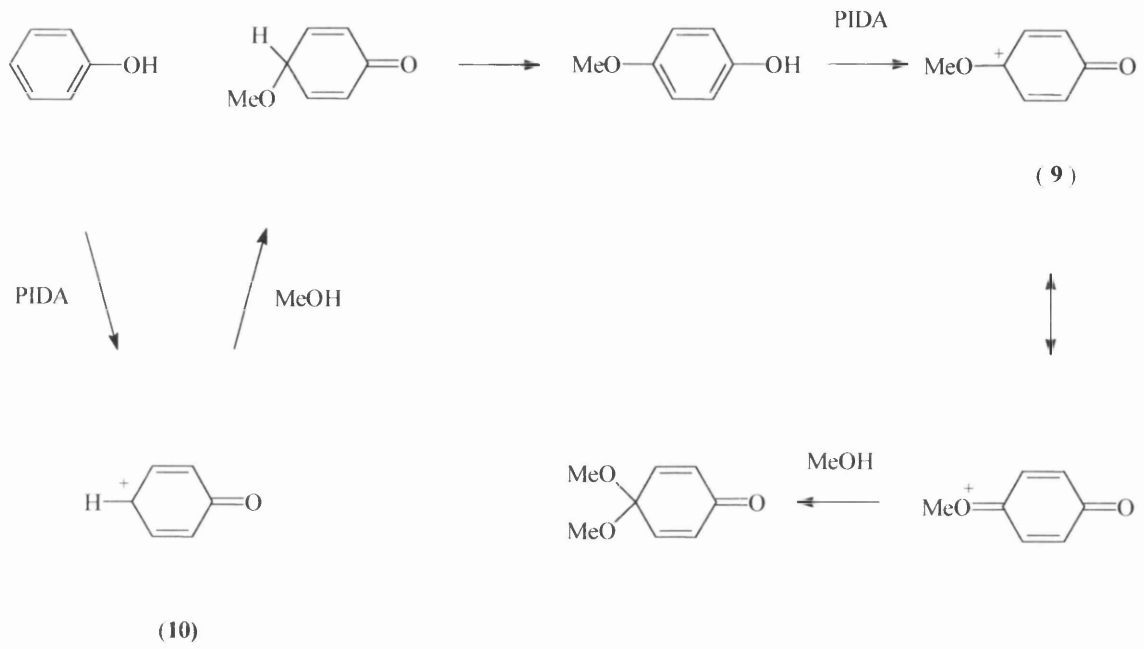
attack occurs at C-2, regardless of the steric situation which would favour attack at C-4 or C-6. On the other hand, in phenols lacking such a substituent, calculation indicates that (**8**) most accurately reflects the species present and that nucleophilic attack is predominantly or exclusively at C-4.

Using path *a* as an example from their findings on the oxidation of phenol, they were unable to stop the reaction at 4-methoxyphenol but obtained 4,4-dimethoxycyclohexa-2,5-dienone instead, even when one equivalent of PIDA was used. The same product was obtained when oxidising 4-methoxyphenol although this reaction proceeded much more rapidly than with phenol.

This result was however to be expected as the phenoxenium intermediate (**9**) would be stabilised by a factor of at least 2000 with respect to phenoxenium ion (**10**) (Scheme 6).

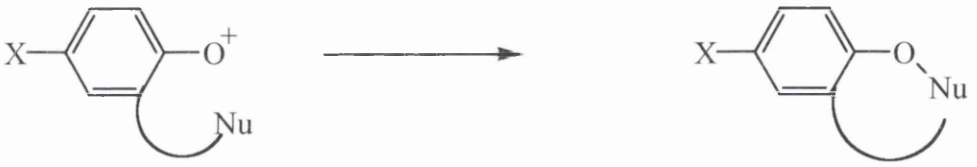
Both results are in line with predictions based on the charge distributions and LUMO coefficients for phenoxenium ions. Attack at C-2 occurs on oxidation of 2-methoxyphenol even though this is the most hindered position, again in line with the tables' predictions.

3,5-Dimethoxyphenol oxidises at C-4 despite the hindrance at this position. Also observed were 2,3-dimethoxyphenol substituting at C-4 whilst 2-methoxy-4-methylphenol substitutes at C-2 showing how effective a methoxy group is at stabilising a positive charge. 4-benzylphenol also oxidises at C-4 despite severe steric hindrance. In the case of cations derived from phenol and alkylphenols, the greatest concentration of charge always appears at C-4.

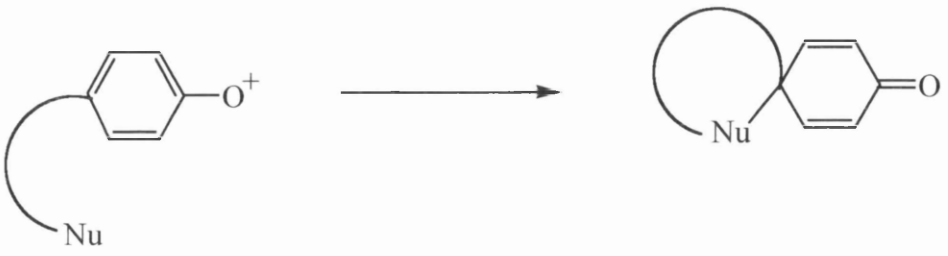


Scheme 6

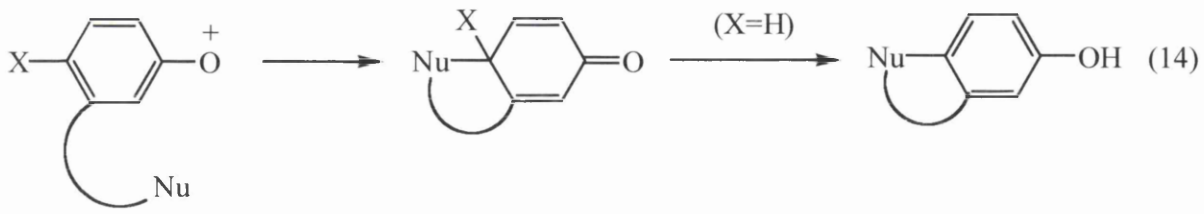
In view of the above, a number of general reactions could be envisaged using intramolecular nucleophilic attack on phenoxenium ions to form a large range of heterocyclic compounds (eqns. 12, 13 and 14).



(12)



(13)



(14)

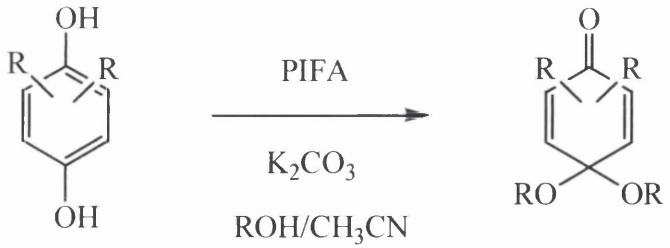
1.6 Phenyliodonium bistrifluoroacetate

1.6.1 Phenyliodonium bistrifluoroacetate

Another commercially available hypervalent iodine compound, phenyliodosyl bis trifluoroacetate (PIFA), ($PhI(OCOCF_3)$, has also been used recently as an oxidising agent.[33,34,35,36]

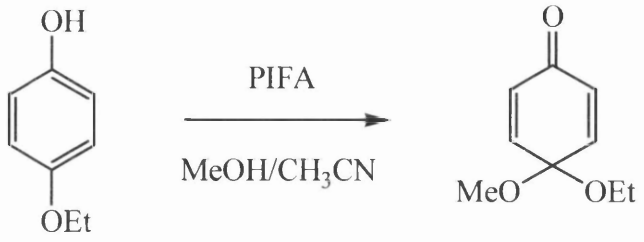
1.6.2 Oxidation of *p*-alkoxyphenols

Like PIDA, PIFA was shown to react with various types of *p*-alkoxyphenols to give the corresponding *p*-benzoquinone monoactetals in excellent yields under mild conditions (eqn.15)[37]. The compounds are attractive in organic synthesis as they can serve as precursors to various types of natural products such as tropolones, α-tocopherol and anthracyclines.



(15)

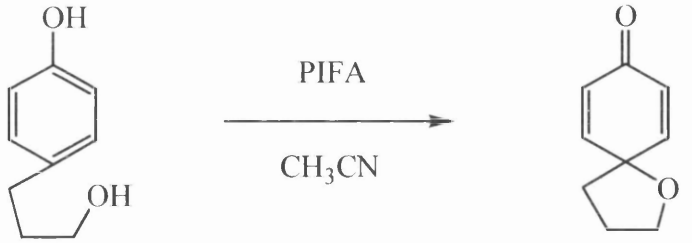
Work was extended to other phenols to yield unsymmetrical monoacetals of *p*-benzoquinones in high yields (eqn.16).



(16)

1.6.3 Intramolecular cyclisations to form spiro compounds

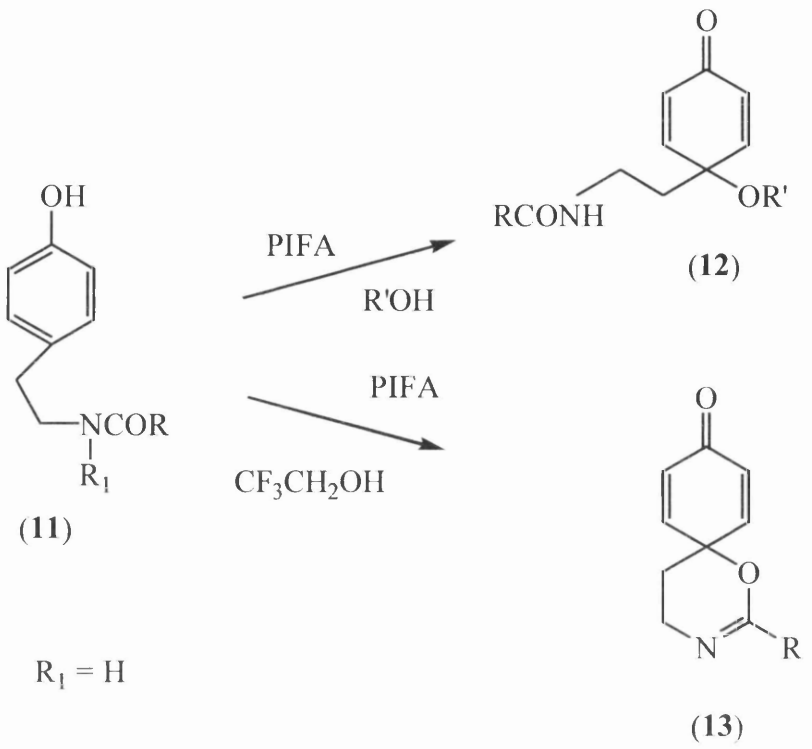
Intramolecular ipso trapping by some nucleophiles such as carboxy, hydroxy and amido groups has also been achieved which all lead to their corresponding spiro compounds (eqn.17) [37]



(17)

1.6.4 Oxidation of N-acyltyramines

Kita *et al.*[25] have also shown how PIFA has been very useful in converting *para*-substituted N-acyltyramines to the corresponding quinol ethers or spirocyclohexadienone derivatives depending on the solvent medium used in the oxidation (Scheme 7). In nucleophilic solvents such as alcohol or acetic acid, the solvent (nucleophile) attacks the para position of (**11**) to yield the quinol ether derivative (**12**).



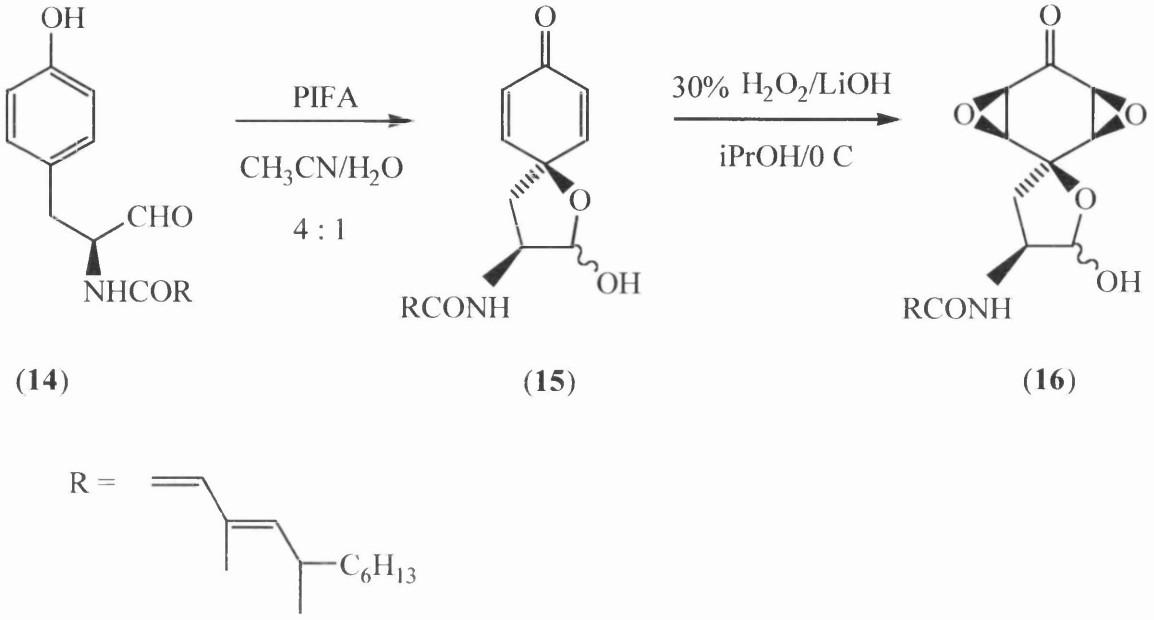
Scheme 7

A number of alcohols were used e.g. ethanol, 2-propanol etc all yielding the corresponding quinol ethers fairly rapidly. Other phenols in similar solvents also reacted with PIFA to give the corresponding quinol ethers. In poorly nucleophilic solvents such as 2,2,2-trifluoroethanol or dichloromethane in the presence of potassium carbonate, cyclisation occurs *via* attack on the amido group to give the spirocyclohexadienones (**13**). Spirodienone derivatives form part of the structure of many pharmacological compounds aswell as being very useful synthetic intermediates in organic chemistry.

1.6.5 Oxidation of n-acylated aldehydes

McKillop *et al.*[38] used the above methodology to good effect in the synthesis of the antibiotic aranorosin (**16**). They oxidised *N*-acylated tyrosine aldehydes (**14**) in aqueous

solvent to give the required aranorosin precursor lactols (**15**) via a very concise route (Scheme 8).

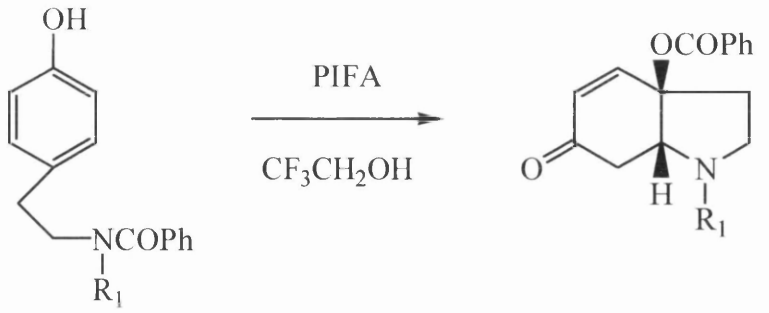


Scheme 8

Tyrosine derivatives have also attracted attention from others[39,40] who have also incorporated hypervalent iodine reagents in their syntheses.

1.6.6 Oxidation of *N*-alkyl-*N*-benzoyltyramines

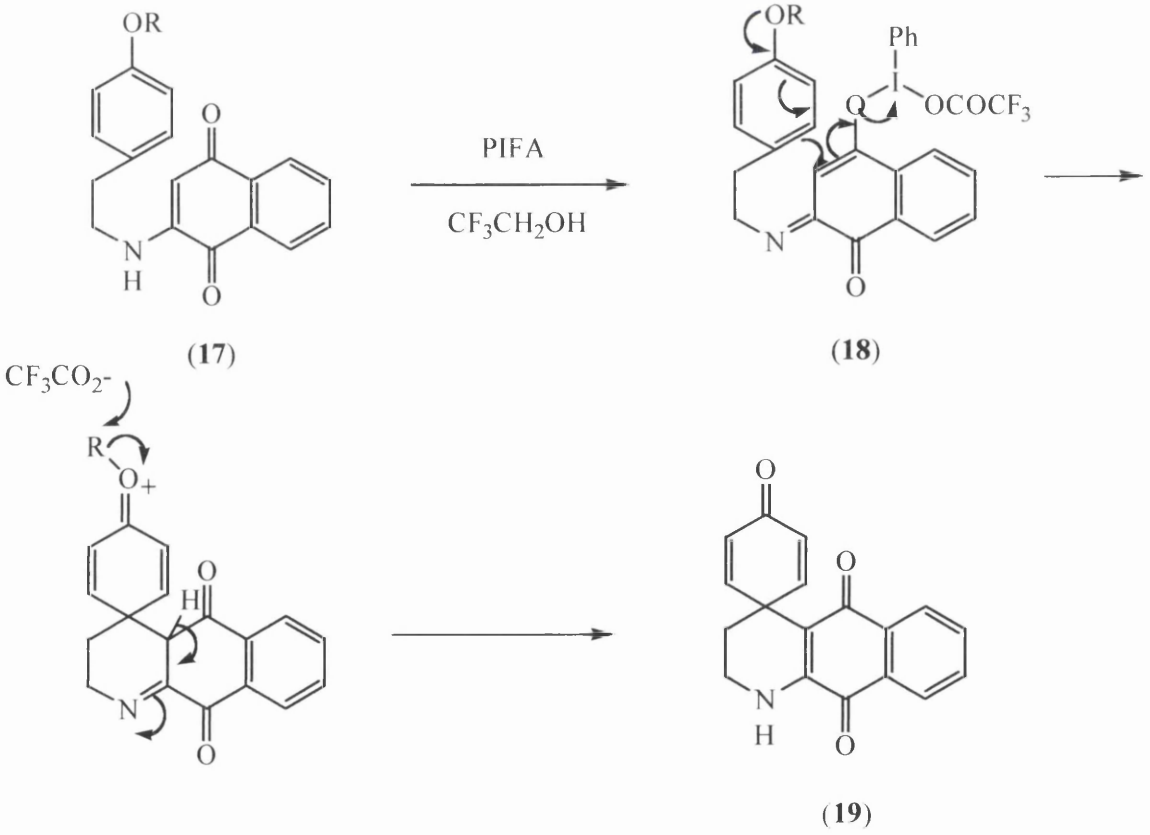
PIFA was also used to oxidise *N*-alkyl-*N*-benzoyltyramines[25] which yielded the corresponding hexahydroindol-6-ones when used in conjunction with 2,2,2-trifluoroethanol, followed by aqueous workup (eqn. 18).



(18)

1.6.7 Oxidation of *O*-silylated phenolic derivatives with aminoquinones in the *para* position

Oxidation of *O*–silylated phenolic derivatives with aminoquinones in the *para* position has been achieved with PIFA to synthesise a series of azacarbocyclic spirodienones (Scheme 9).[41] Kita suggests that PIFA reacts with the aminoquinone moiety of the substituted phenol derivative (**17**) to give the intermediate (**18**), which can then cyclise to give the spirodienones, probably due to the ready cleavage of the R-O bond of the spirodienone intermediate by nucleophilic attack of the generated trifluoroacetoxy anion.



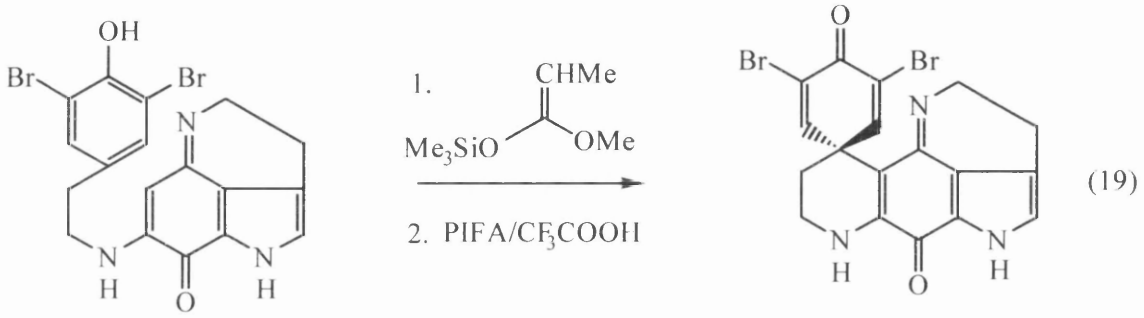
(**17**) (**18**)

(**19**)

R=H, TMS, TBDMS, Me Scheme 9

The significance of these resulting spirodienones and the methodology that has been used, was applied by Kita in the synthetic approach to discorhabdin C (eqn.19).[42]

Discorhabdin C comes from a group of alkaloids isolated from the sponge *latruncula du bocage* in New Zealand, which exhibit extreme toxicity towards tumor cells (P388 and 1210 leukemia) and has a unique molecular skeleton incorporating an azacarbocyclic dibromocyclohexadienone system and a highly oxidised indole system in which the tryptamine side chain is cyclised into an indoloquinone.

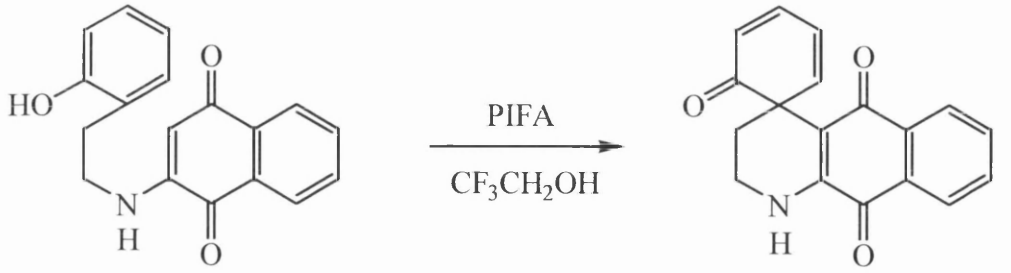


(19)

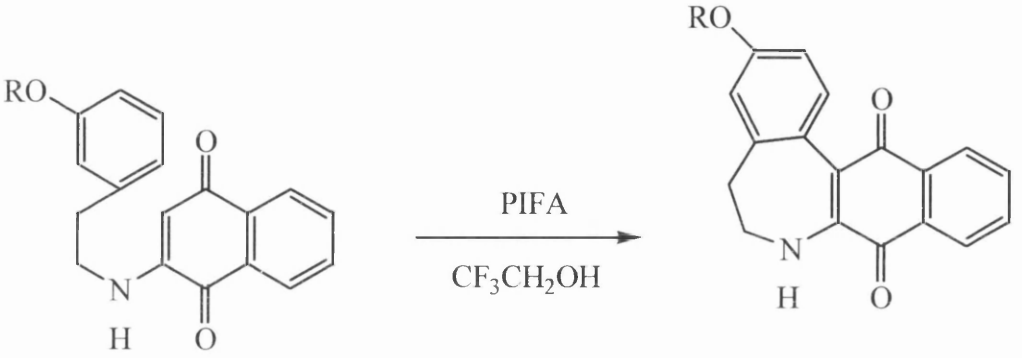
Discorhabdin C

1.6.8 Oxidation of *O*-substituted phenolic derivatives with the aminoquinones in the *ortho* and *meta* positions

Kita has also reported the intramolecular cyclisation of various phenol derivatives bearing aminoquinones at the *ortho* and *meta* positions and has shown how PIFA oxidation can provide a versatile route to a number of difficult to obtain heterocyclic compounds (eqns. 20 and 21)[43].



(20)

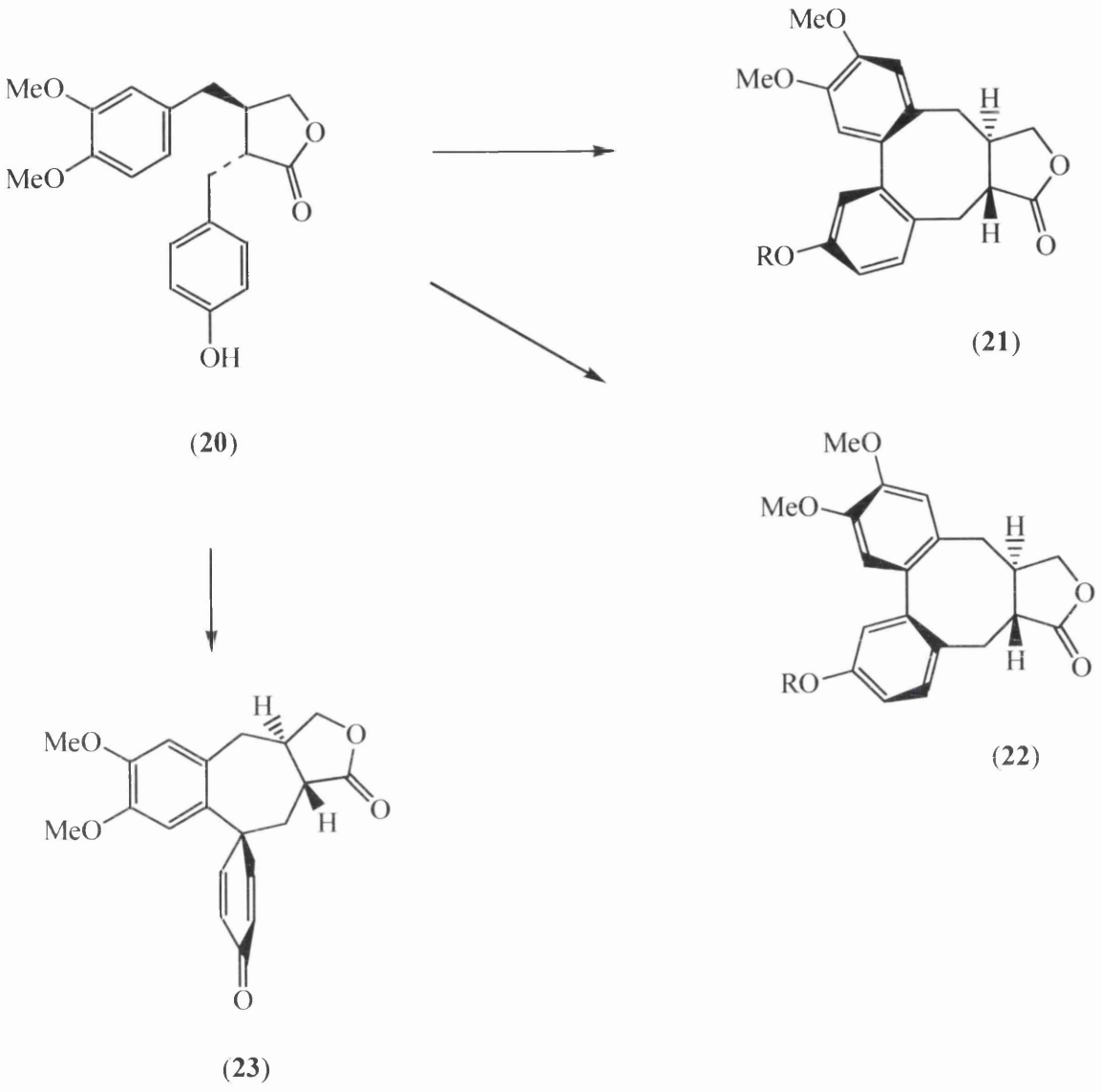


(21)

R = TBDMS, Me, H,TMS

1.6.9 Oxidation of phenolic dibenylbutyrolactones

Dibenzocyclooctadienes (**21** and **22**) and spirodienones (**23**) have also been made by PIFA oxidation in 2,2,2-trifluoroethanol, the products being dependent on the length of time of the reaction[27]. This reaction follows from those general equations postulated by Pelter[33] for nucleophilic intramolecular trapping (eqn. 13). The nucleophile in this case being an activated benzene ring (**20**) attached by a carbon chain to the C-4 position of the phenol being oxidised (Scheme 10). The spirodienone compounds obtained have been proposed as intermediates in the synthesis of dibenzocyclooctadiene lignans. These reactions seem to also offer a rapid biomimmetic route to other compounds in the dibenzocyclooctadiene series.



(**20**) (**21**) (**22**) (**23**)

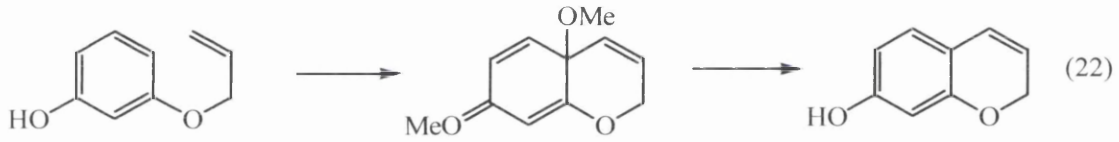
Scheme 10

Chapter 2

PIDA Oxidation of 3-Substituted Phenols

2.1 Aim of the project

The aim of this project was to synthesise substituted phenols with a nucleophilic chain linked to the *meta* position to the phenolic hydroxyl group. The nucleophile utilised initially was an olefin linked by a methyleneoxy group to the phenol. It was envisaged, that the olefinic nucleophile would undergo intramolecular cyclisation in the 4 position by generating the phenoxenium ion obtained by PIDA oxidation of (**24**) to give the corresponding chromenone (**25**), and subsequent chromene (**26**), (eqn 22). Chromenes are valuable building blocks to a number of heterocyclic compounds and have generated a great deal of interest over the years.[44-47]

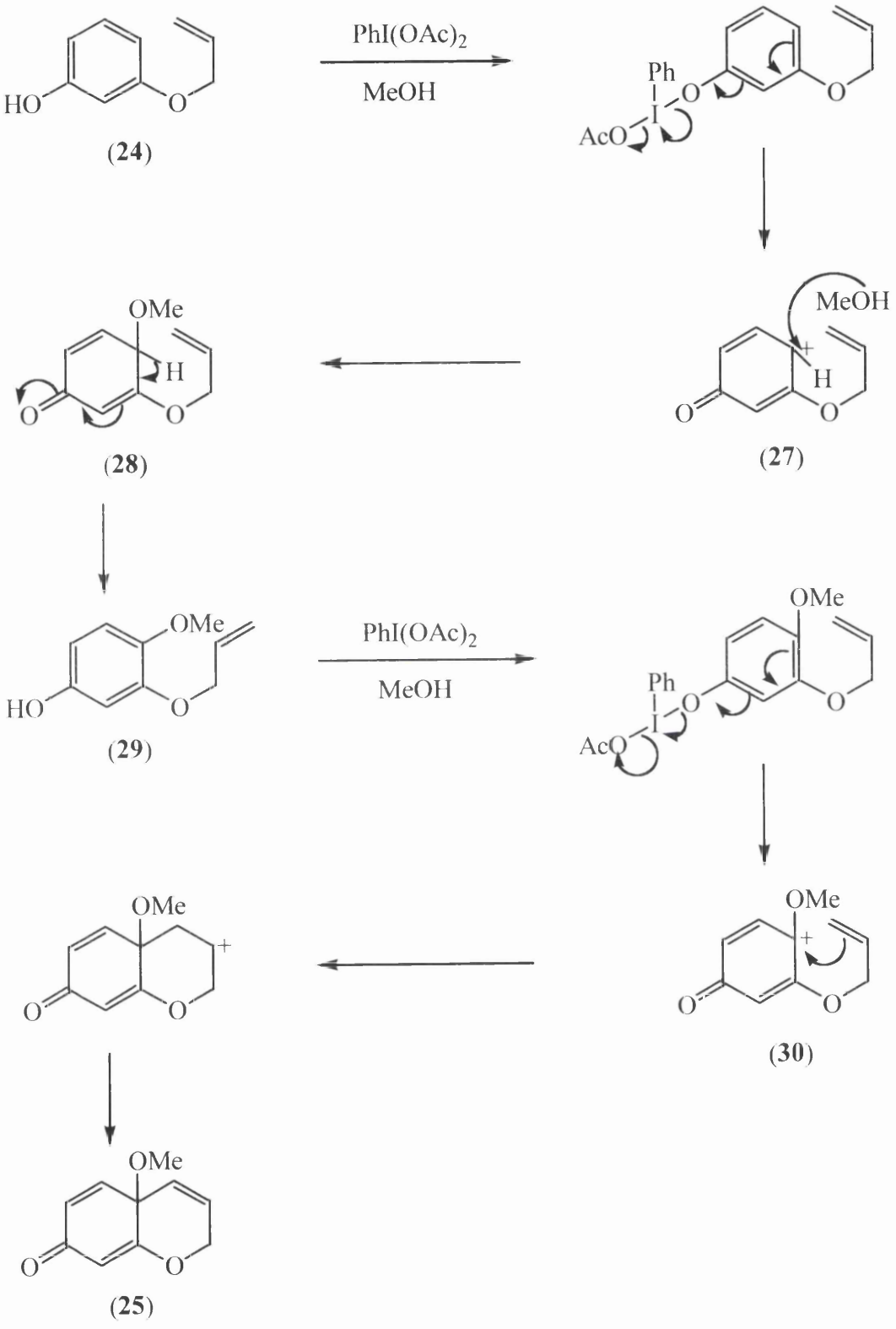


(22)

(**24**) (**25**) (**26**)

2.2 The proposed mechanism of the reaction

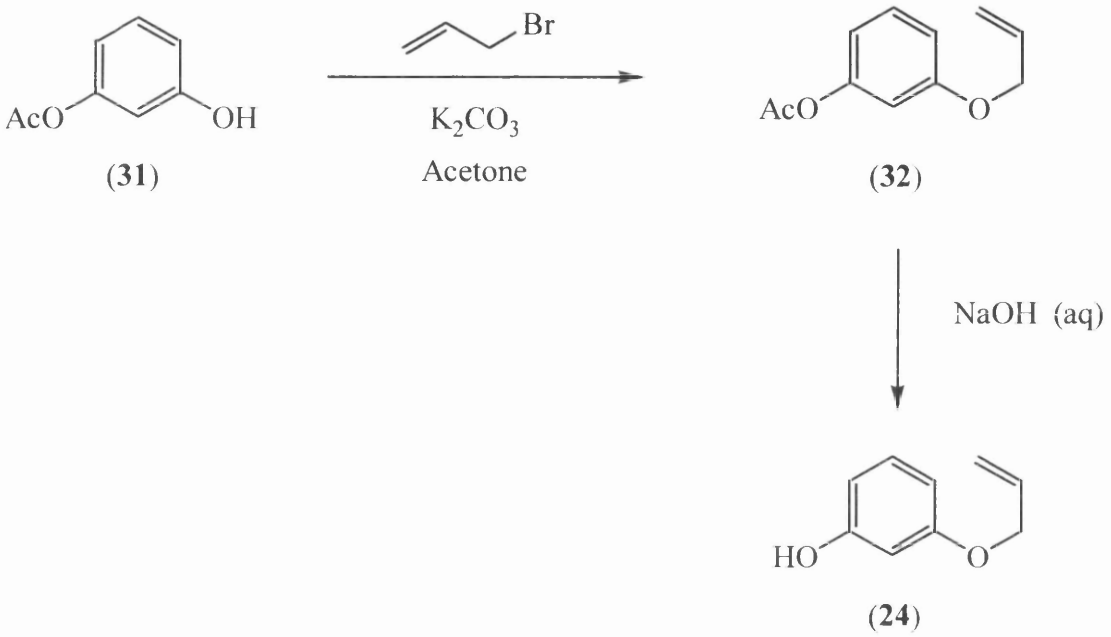
The proposed mechanism for the reaction outlined above in eqn.22 follows from that postulated in section (1.5), whereby attack on 3-allyloxyphenol phenol (**24**) by 1 equivalent of PIDA, (scheme 11), would first give phenoxenium ion (**27**). Upon attack of external nucleophile MeOH, quinone intermediate (**28**) would be formed, which may undergo enolisation to the equivalent 4-methoxyphenol intermediate (**29**). Attack by another equivalent of PIDA should give the more stable phenoxenium ion (**30**) to which the olefin could react intramolecularly to give chromenone (**25**).


PhI(OAc)2
MeOH
HO
O
(24)
Ph
I
O
AcO
MeOH
OMe
H
(28)
(27)
PhI(OAc)2
MeOH
(29)
(30)
(25)

Scheme 11

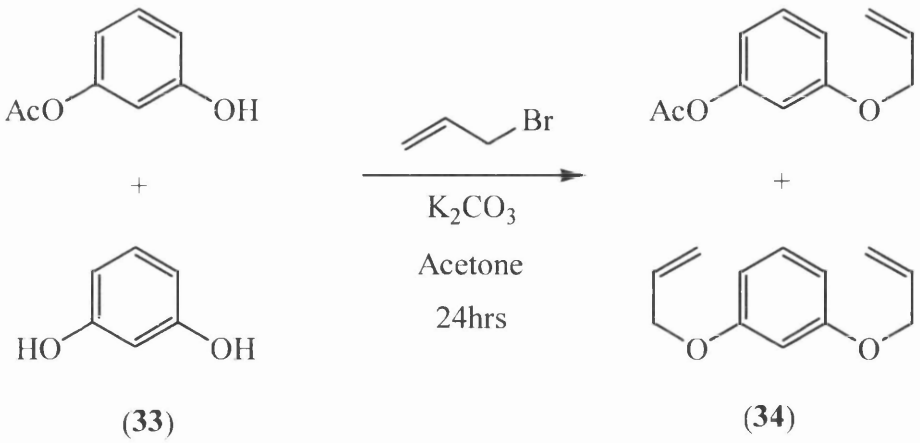
2.3 The preparation of 3-allyloxyphenol (24)

The desired phenol was to be prepared by a two step synthesis, starting from commercially available resorcinol monoacetate (**31**) and allyl bromide (Scheme 12).[48]



Scheme 12

Initial attempts to prepare the ether (**32a**) from commercially available resorcinol monoacetate (**31**) proved difficult due to the fact it was contaminated by resorcinol (**33**) despite repeated distillations. This resulted in significant amounts of the diallyl ether (**34**) being formed. (Up to 35% of total reaction yield, Scheme 13).

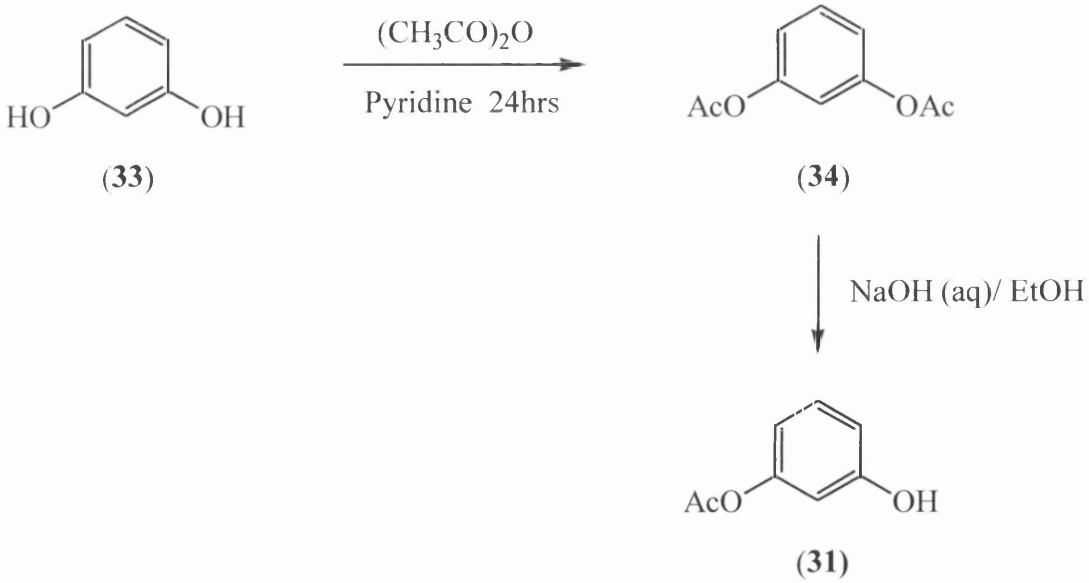


(**33**) (**34**)

Scheme 13

2.3.1 The preparation of resorcinol monoacetate (**31**)

Resorcinol diacetate (**34**) could be obtained (>98% yield) by protection of both phenolic hydroxyl groups of resorcinol (**33**) by reaction with excess acetic anhydride in pyridine. Selective hydrolysis was effected using 2M NaOH in ethanol to provide the desired monoacetate (**31**) in yields of up to 47 % (Scheme 14), of pure material.

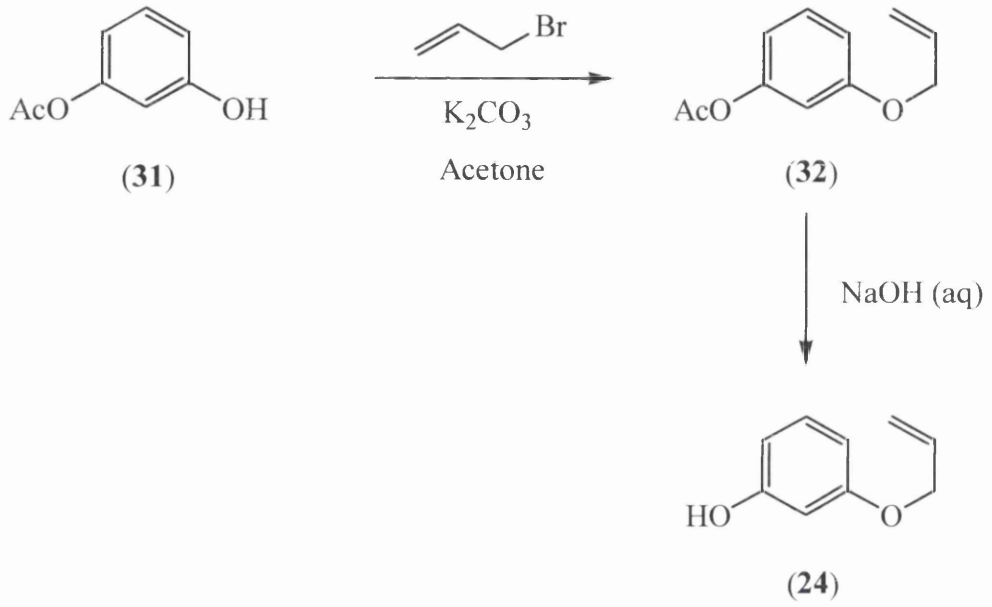


(**33**) (**34**) (**31**)

Scheme 14

2.4 Preparation of 3-allyloxyphenol(24) using freshly prepared resorcinol monoacetate

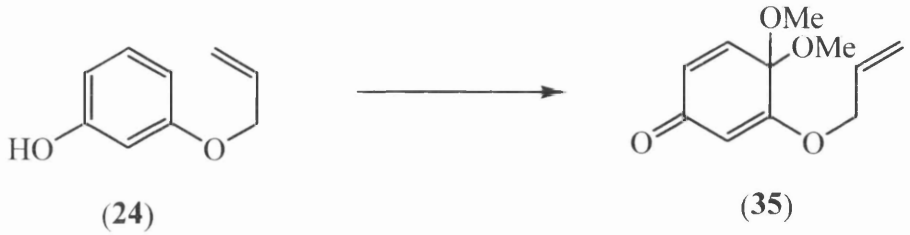
Addition of freshly prepared monoacetate with allyl bromide gave the corresponding ether (**32**) in good isolated yield (78%) and subsequent deprotection of the acetate by aqueous base provided the required phenol (**24**) again in good yield (82%) (Scheme 15).



Scheme 15

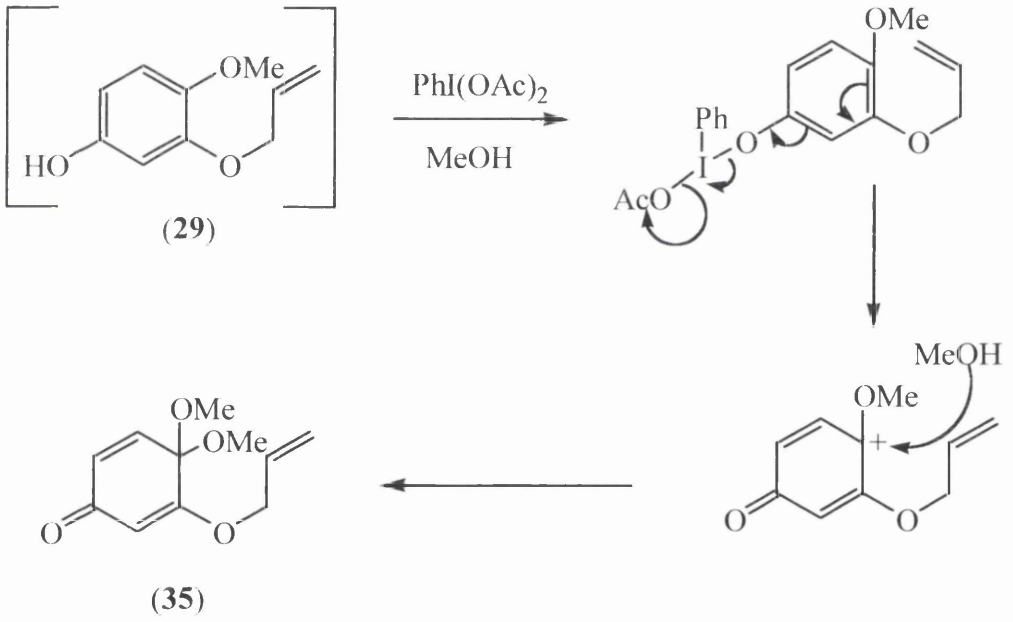
2.5 The Oxidation of 3-allyloxyphenol (24)

With the 3-substituted phenol (**24**) in hand, attention was then focused on effecting the nucleophilc intramolecular cyclisation at the C-4 position. Unfortunately reaction of phenol (**24**) with one equivalent of PIDA in anhydrous methanol gave 4,4-dimethoxyquinone (**35**), not the expected chromenone (**25**), as well as providing unreacted starting material (**24**). When two equivalents of PIDA was employed all starting material was consumed and (**35**) was isolated in 33% yield (eqn 23).



(24) (35) (23)

Instead of following that route postulated in Scheme 11, it appears that on the assumed formation of 4-methoxyphenol (**29**), attack is at the C-4 position by methanol and not the attached nucleophilic side chain (Scheme 16).



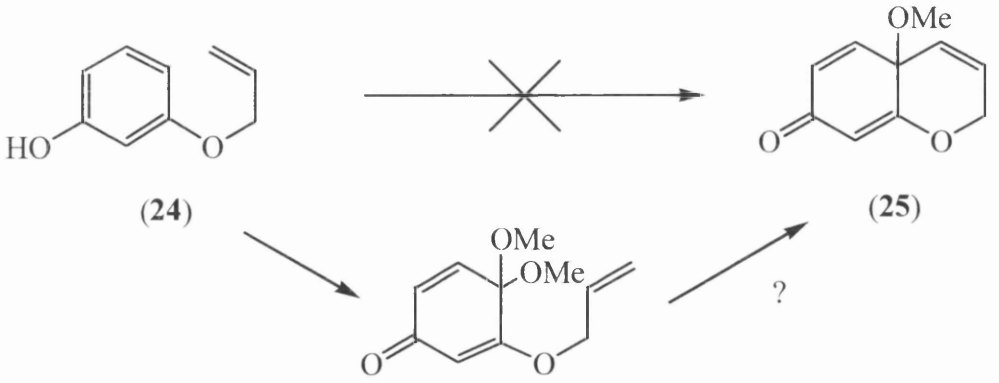
Scheme 16

The formation of the 4,4-dimethoxycyclohexa-2,5-dienone (**35**) brought into question either the degree of nucleophilicity of the olefinic group and/or the lack of steric restriction in the linker unit. After 24hrs, the dienone (**35**) showed signs of decomposition by HPLC analysis indicating that it was a labile species.

2.6 Acid catalysed reactions of 3-allyloxy-4,4-dimethoxycyclohexadien-2,5-one (35)

Due to the reactive nature of dienone (**35**) it was postulated that this would be a suitable intermediate for ring closure to give chromenone (**26**), as it has been shown[49] that Lewis acid catalysed reactions can cause ring closure between alkenes and quinone methides to give a variation in cyclisation products, albeit intermolecularly. It is also known that phenoxenium ion (**30**) is more stable than (**27**)[18] and so on production of this reactive intermediate in a less nucleophilic solvent than methanol it was hoped the olefin would cyclise to the electron deficient C-4 position on the phenol to give chromenone(**26**).

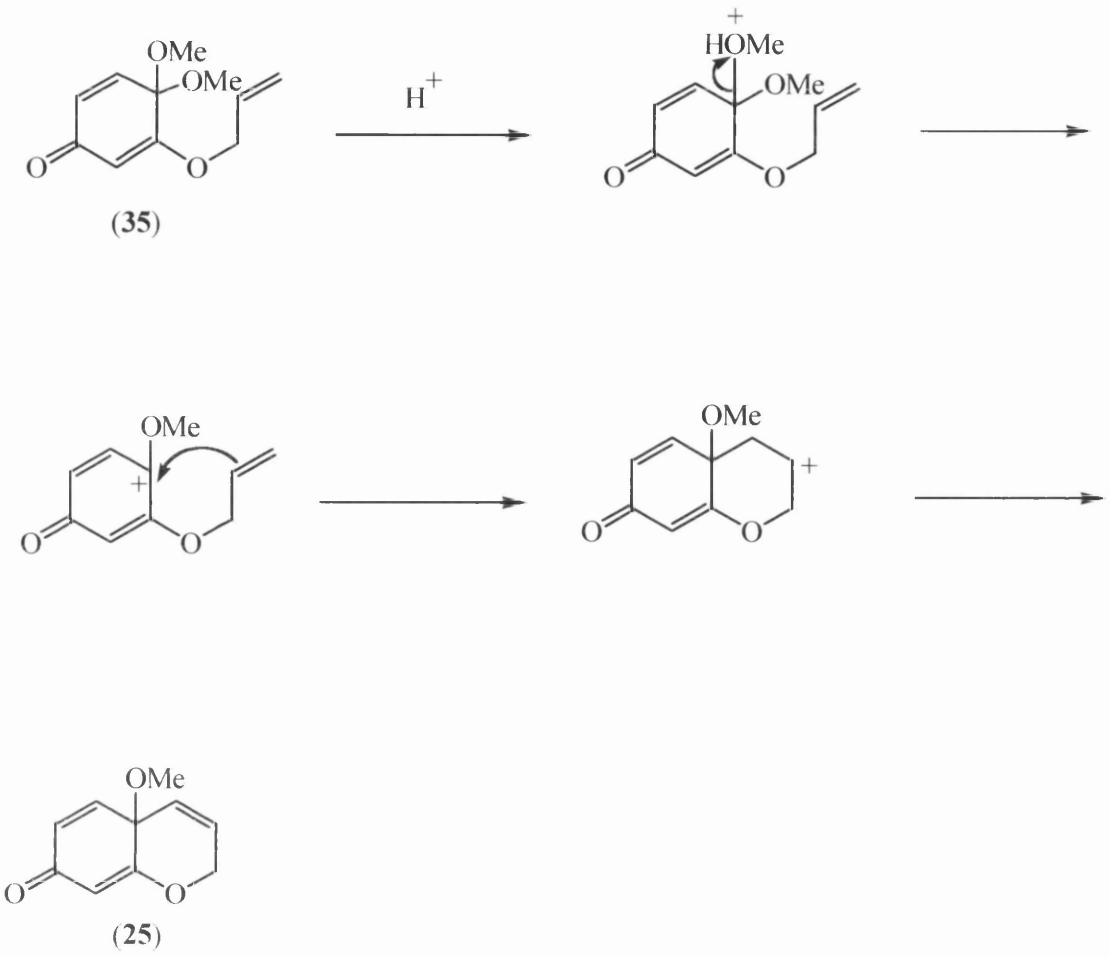
Therefore, we treated (**35**) with a variety of acids to see if the cyclised product (**25**) could be obtained in a two rather than a one step reaction (Schemes 17 and 18)



(**24**) (**25**)

(**35**)

Scheme 17



(35)

(25)

Scheme 18

2.7 The reaction of dienone (35) with various Lewis and protic acids

A variety of Lewis and protic acids were used to instigate cyclisation of dienone (**35**). They were BF_3OEt_2, *p*-TSA, $TiCl_4$, Amberlite resin acid, TFA, $HClO_4$, MeSOH, $ZnBr_2$, $(Me)_2AlCl$ and $MgBr_2$. All acids used were the highest purity grade available used straight from the bottle or were used immediately after purification.

The reactions were carried out at –78 °C, under nitrogen, with constant stirring and involved the dienone being dissolved in a small amount of non nucleophilic solvent such as dichloromethane or diethyl ether. One equivalent of the purified acid in the

same non nucleophilic solvent was then added dropwise to the reaction via a double ended needle. The reactions were followed every 10 minutes by hplc and tlc. See Table 1.

Once reaction had taken place, scale up reactions were carried out.

Some acids reacted differently to others. Using BF_3OEt_2 , $TiCl_4$ and $(Me)_2AlCl$, reaction was very quick and the resulting hplc traces of the reactions showed many peaks had formed. Attempted separations were carried out on a chromatotron or by column chromatography but proved fruitless as mixtures were always obtained and the resulting nmr spectra gave no identifiable products at all.

Methane sulphonic acid (MeSOH) and $HClO_4$ reacted immediately with the dienone both giving by far the most complicated hplc traces. Many products were formed indicating complete breakdown of compounds. Nevertheless attempts were made to separate any compounds but again non identifiable mixtures of products were obtained.

p-TSA, TFA, $ZnBr_2$ and $MgBr_2$ appeared to give encouraging results in that only a few new peaks were seen to have formed on addition of the acid to the dienone. Scale up and separation showed many products had actually formed however none could be isolated. The resin acid showed no signs of reaction even after a couple of days and when stopped, starting material was recovered.

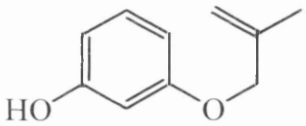
One possibility to aid identification would have been to set up some form of GC-MS apparatus to see if any products could be identified this way.

Acid used	Reaction at -78°C	Reaction at room temp.	Products isolated Reaction comments
BF_3OEt_2	yes	n/a	Very quick rection. Many peaks by hplc. No products isolated.
p-TSA	yes	n/a	Slow reaction. Few new peaks by hplc. No products isolated
$TiCl_4$	yes	n/a	Very quick reaction. Many peaks shown by hplc. No prods isolated.
resin acid	no reaction	no reaction	Starting material recovered
TFA	yes	n/a	Slow reaction. Few new peaks by Hplc. No products isolated.
$HClO_4$	yes	n/a	Instant reaction. Many peaks seen by hplc. None distinguishable. No products isolated.
MeSOH	yes	n/a	As for $HClO_4$ results. Instant reaction. No products isolated
$ZnBr_2$	no reaction	yes	Slow reaction. Thick peaks obtained by hplc. No products isolated.
$(Me)_2AlCl$	yes	n/a	Very quick reaction. Many peaks seen by hplc. No prods. Isolated.
$MgBr_2$	no reaction	yes	Slow reaction. Few peaks seen by hplc. No products isolated

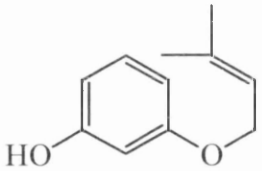
Table 1. Observations of acid catalysed reactions on dienone (**35**)

2.8 Modifying the nucleophilic side chain

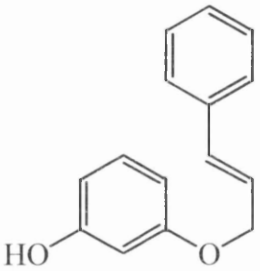
Due to the lack of success in cyclising dienone (**35**) it was decided to modify the olefinic side chain. Attention was focused on incorporating a more nucleophilic side chain. Adding a methyl or phenyl group onto the olefin chain should result in greater nucleophilicity of the olefin due to the enhanced stabilisation of the resulting carbocations . Once the phenoxenium ion had been obtained in the C-4 position the hope was that cyclisation would then occur. The phenols illustrated below were chosen as suitable precursors for cyclisation because they were readily accessible:-



(**36**)



(**37**)



(**38**)

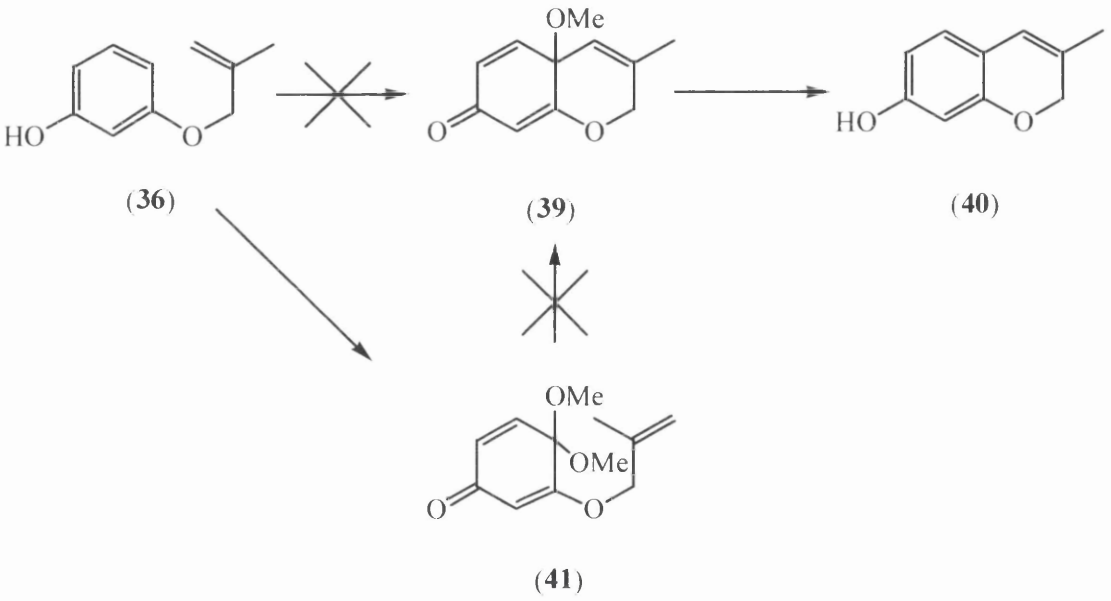
2.9 The preparation of phenols (36), (37) and (38)

Initially the preparation of phenols (**36**), (**37**) and (**38**) was undertaken as for the synthesis of phenol (**24**) in section 2.4 using the equivalent alkyl halides (3-chloro-2-methyl propene to give **32b**, 4-bromo-2-methylbut-2-ene to give **32c** and cinnamyl bromide to give 32d) for each new compound to react with resorcinol monoacetate to give the desired phenylacetates (**32b-d**). Then subsequent deprotection of the acetate group lead to the deired phenols. However, preparation of these phenols (**36**), (**37**) and (**38**) proved a little more difficult than anticipated. The primary reason for this was the fact that the air sensitive

halides that were being used in the reactions were available only in their more stable chloride form. Addition of KI to the reaction mixture overcame these difficulties and improved yields significantly.

2.10 The Oxidation of 3-(2-methylallyloxy)phenol (36)

Oxidation of phenol (**36**) was predicted to give us the chromenone (**39**) which could be reduced to the corresponding chromene (**40**).



(**36**) (**39**) (**40**)

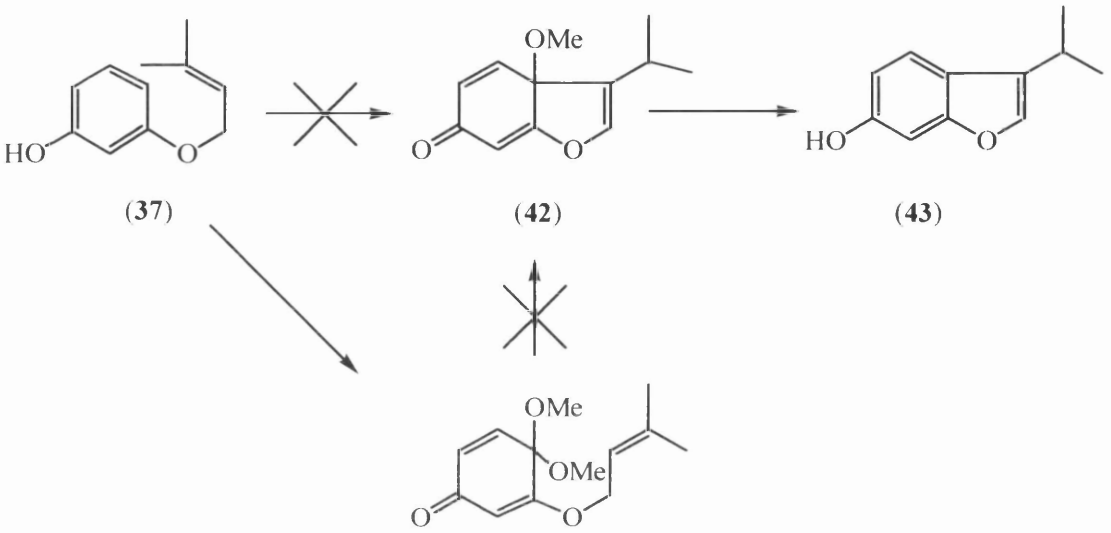
(**41**)

Scheme 19

However, upon oxidation compound (**39**) was not obtained . The oxidation followed the same route as shown in Scheme 19, in which, addition of 1eq of PIDA in MeOH gave compound (**41**) as well as starting phenol (**36**) and 2eq of PIDA gave only compound (**41**) in 37 % yield.

2.11 The Oxidations of 3-(3-methylbut-2-enyloxyl)phenol (37) and 3-(3-phenylallyloxy)phenol (38)

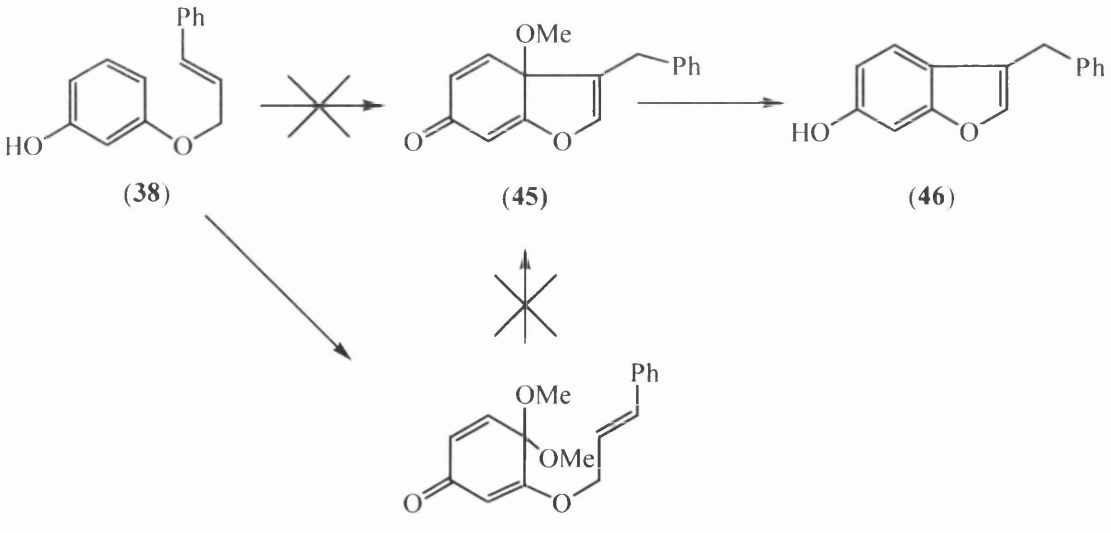
The oxidations of phenols (**37**) and (**38**) were expected to give us (**42**) and (**45**) which we envisage eventually leading to the corresponding benzofurans (**43**) and (**46**).



(**37**) (**42**) (**43**)

(**44**)

Scheme 20



(**38**) (**45**) (**46**)

(**47**)

Scheme 21

Again, predicted compounds (**42**) and (**45**) were not obtained. The oxidations using 1eq PIDA in methanol gave (**44**) and (**47**) together with unreacted (**37**) and (**38**). On addition of 2eq PIDA and following work-up the reactions yielded the corresponding dimethoxy quinone ketals (**44**) and (**47**) in low yields (19 and 48 % respectively).

2.12 Acid catalysed reactions on dimethoxyquinones (41), (44) and (47)

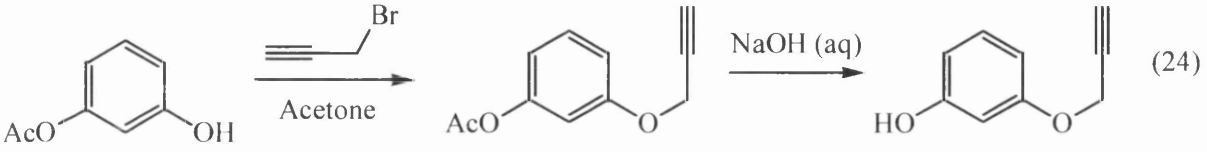
Acid catalysed reactions (see section 2.7),were tried to cyclise these quinone ketals in the hope that the added nucleophilicity would allow the olefin to react with the envisaged positive phenoxenium , (scheme 11), ion to give the desired compounds (**39**), (**42**) and (**45**). Reaction occurred rapidly and many products were formed as shown by HPLC. Attempts to separate compounds out from those reactions that showed promising results were done however no products could be isolated.

2.13 Oxidation of phenols (36), (37) and (38) in different non nucleophilic solvents

Oxidations of the above phenols were carried out in different solvents in the hope that as they are less nucleophilic than methanol, this would allow attack by the nucleophilic side chain onto the C-4 position of the envisaged phenoxonium ion. The solvents used were 2,2,2-trifluoroethanol, trifuoroacetic acid, dichloromethane, acetonitrile and hexafluoroisopropanol. PIFA as well as PIDA was used as a variant of the oxidising agent. All reactions attempted gave unidentifiable polymeric products.

2.14 Preparation of 3-prop-2-ynyloxyphenol (49)

The replacement of the alkene group by the more nucleophilic alkyne was of interest. The proposed acetylenic 3-substituted phenol (**49**) could be made from readily available starting materials.



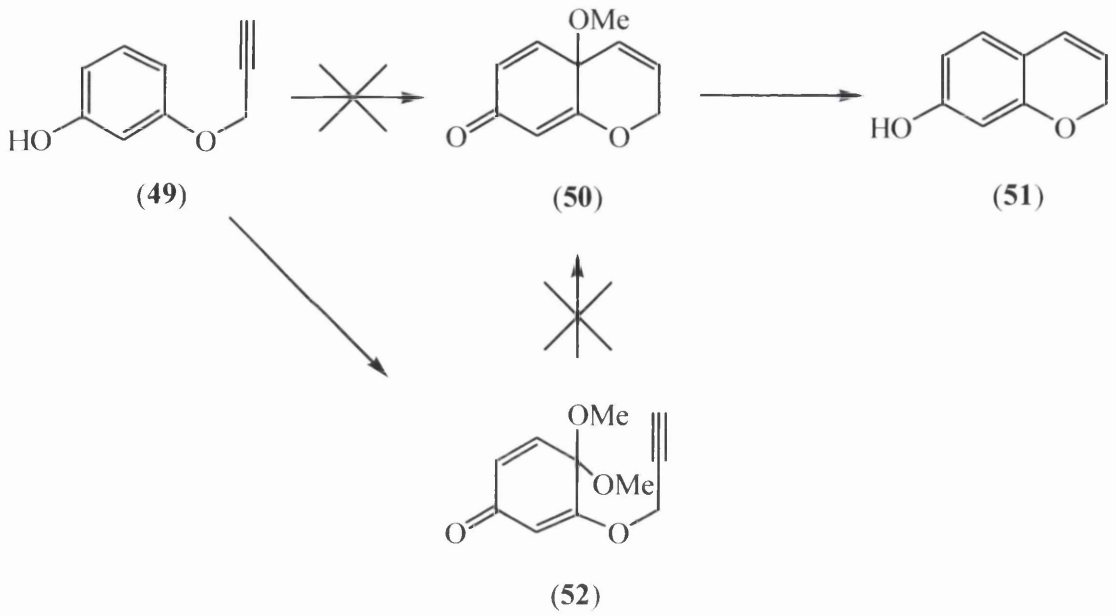
(24)

(**31**) (**48**) (**49**)

Employing a modification of the previously established methodology for constructing the cyclisation precursors (section 2.4), reaction of resorcinol monoacetate (**31**) with propargyl bromide generated the corresponding ether (**48**) in 59 % yield. Deprotection of the acetate group with aqueous sodium hydroxide gave the desired phenol (**49**) in 85 % yield.

2.15 Oxidation of 3-prop-2-ynyloxyphenol (49)

Phenol (**49**) was now subjected to PIDA oxidation. On addition of 1eq PIDA, a single new peak was seen on the HPLC trace as well as starting material still present. Addition of another equivalent of PIDA enhanced the new peak on the trace whilst the starting material disappeared. After work-up and purification on a silica column, identification of the product obtained showed the oxidation had not yielded the desired chromenone (**50**) but gave only the corresponding 4,4-dimethoxyquinone (**52**)
in 51 % yield.



(49) (50) (51)

(52)

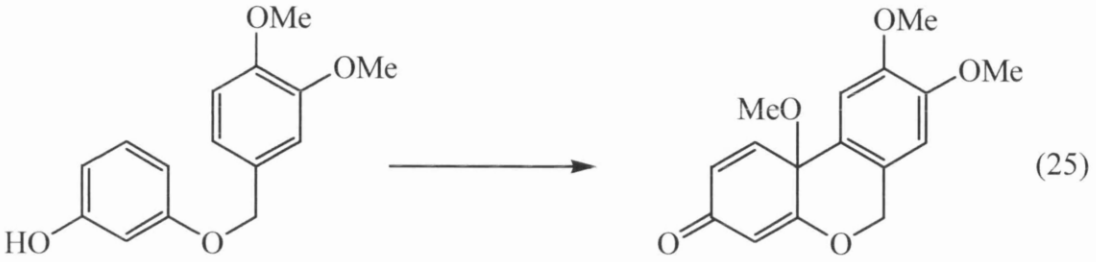
Scheme 22

2.16 Acid catalysed reactions on cyclohexadienone (52)

Acid catalysed reactions on (**52**) as employed earlier in section 2.7 proved unrewarding as complex mixtures were again obtained and individual compounds could not be isolated. Oxidations in other solvents, (see section 2.13) were also carried out on (**52**) but again unidentifiable polymeric products were obtained.

2.17 Increasing the nucleophilic strength of the side chain using aromatic groups

Simple olefinic side chains were not giving the desired chromenones so it was thought that by having a more nucleophilic side chain incorporating aromatic groups with electron releasing groups at C-3 the desired cyclisation products such as (**54**) might be obtained.

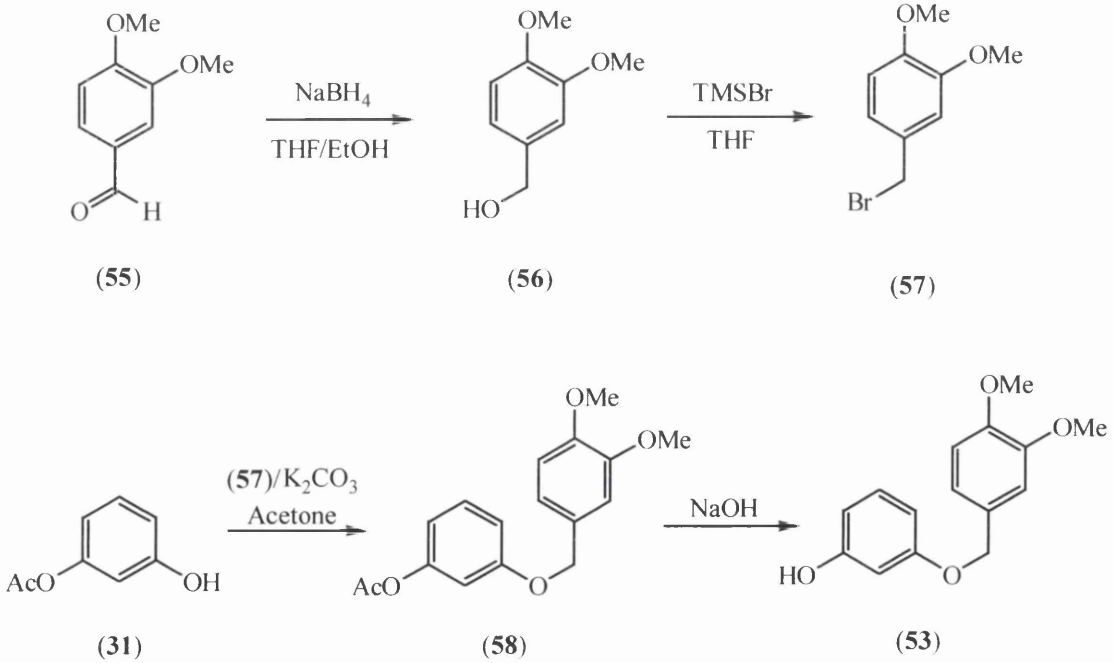


(25)

(53) (54)

2.18 Preparation of 3-(3,4-Dimethoxybenzyloxy)-phenol (53)

Veratraldehyde (**55**) was quantitatively reduced using $NaBH_4$ in THF and ethanol to give veratryl alcohol (**56**) (>98 % yield). On reaction with TMSBr in THF, the alcohol gave the corresponding bromide (**57**) in 93 % yield. Subsequent reaction of the bromide with resorcinol monoacetate (**31**) gave the desired ether (**58**) in 76 % yield. The phenol (**53**) was obtained in 83 % yield by saponification of the ether using NaOH (aq) as described earlier. (section 2.2), Scheme 23.



Scheme 23

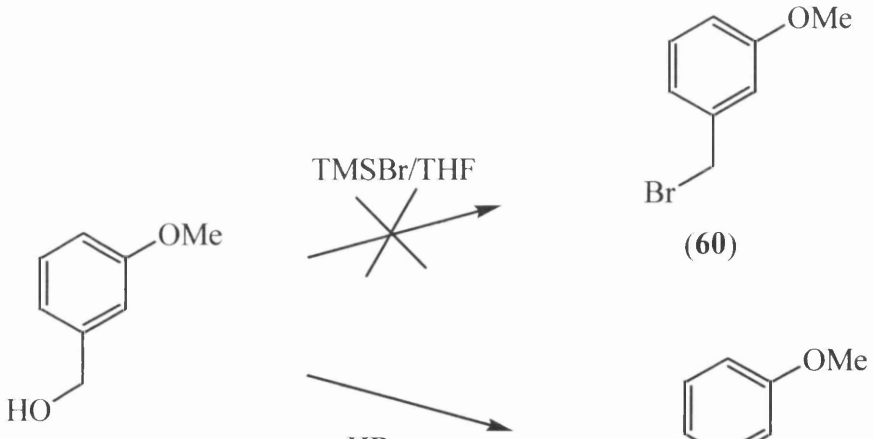
2.19 Oxidation of Phenol (53)

Reaction of (**53**) in methanol with one equivalent of PIDA gave a complicated HPLC trace. Starting material could still be seen so another equivalent of PIDA was added. HPLC then showed no traces of starting material and the other peaks appeared to be enhanced.

Column chromatography and a chromatotron were used to try to separate out the products. No new products could be isolated. A small amount of veratryl alcohol (**56**) was separated from the reaction mixture indicating breakdown of the starting material.

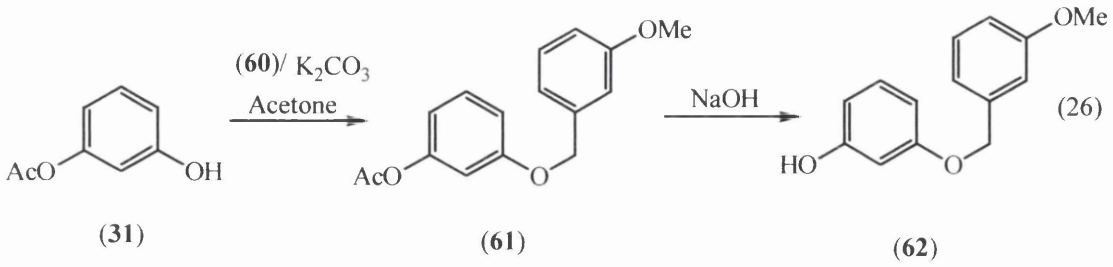
2.20 Preparation of alcohol (62)

We attempted to rectify the problem in section 2.18 by using the 3-methoxybenzyl alcohol (**59**) as opposed to veratryl alcohol since this would remove the problem encountered above. Commercially available 3-methoxybenzyl alcohol (**59**) was initially subjected to TMSBr to give a poor yield of the desired bromide (**60**) and a number of unidentified side products. This approach was abandoned and the more conventional method of using HBr was used and yielded 83% of 3-methoxybenzyl bromide (**60**).



(**59**) (**60**) (**60**)

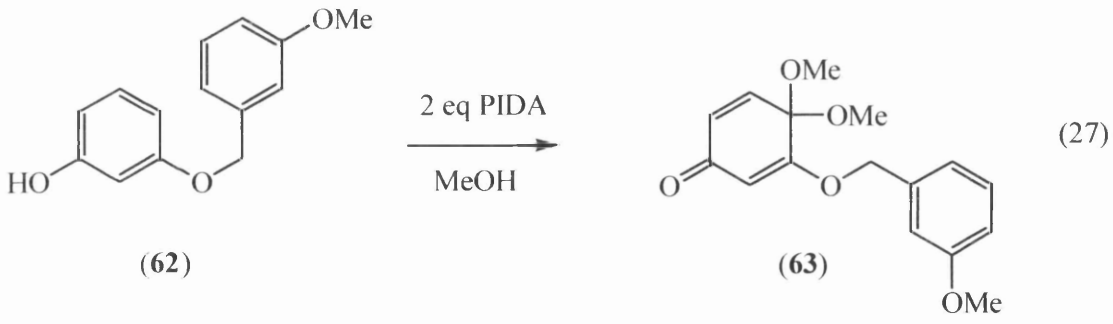
Reaction of bromide (**60**) with resorcinol monoacetate (**31**) gave 80 % yield of ether (**61**) and deprotection of the acetate group with NaOH (aq) gave phenol (**62**) in 82 % yield (eqn. 26)



(31) (61) (62) (26)

2.21 Oxidation of Phenol (62)

Addition of 1eq PIDA to phenol (**62**) gave a single new peak on the HPLC trace as well as starting material. Another eq of PIDA was added to give a single peak and HPLC showed that all starting material had been consumed. Work up and column chromatography gave the 4,4-dimethoxyquinone (**63**) in 39 % yield.



(62) (63) (27)

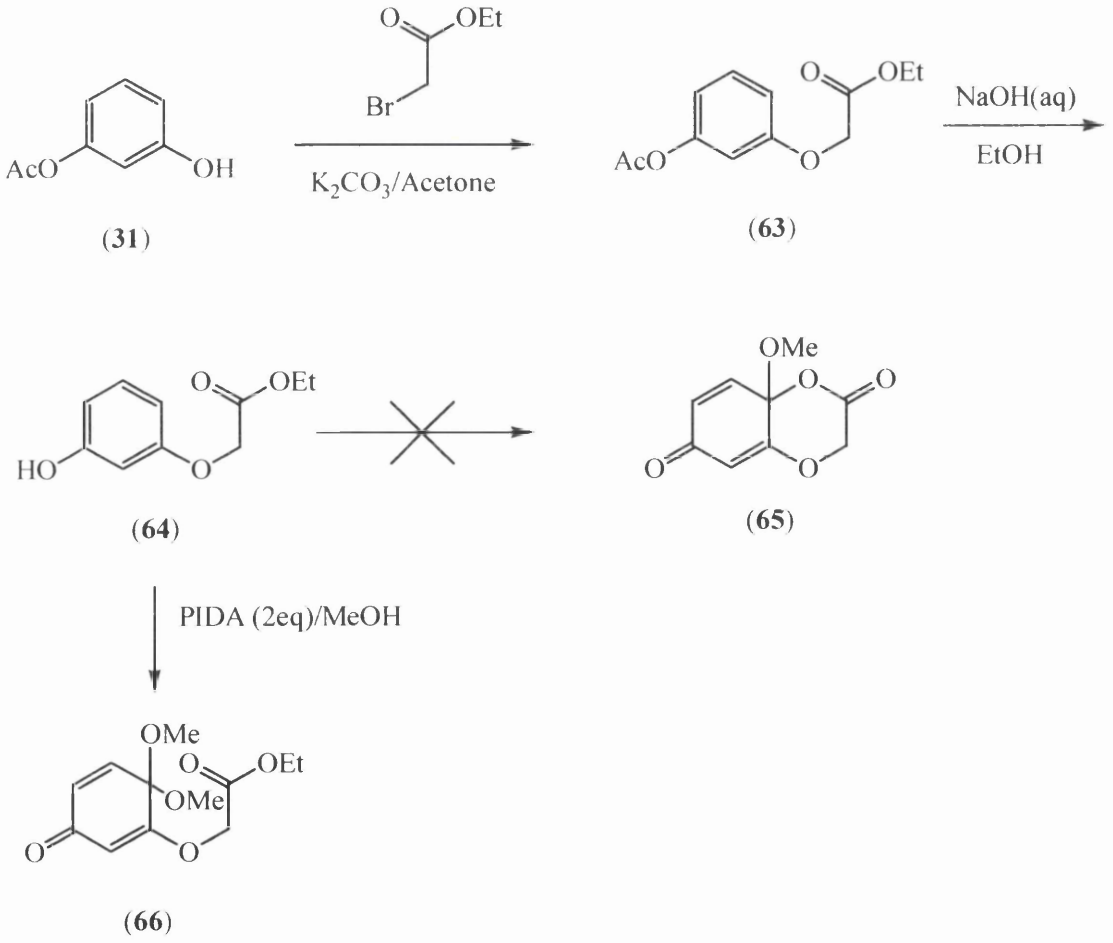
2.22 Acid catalysed reactions on dimethoxyquinone (63)

Again, acid catalysed reactions were undertaken (see section 2.7) but no products could be isolated from the complicated reaction mixtures. Further oxidations of (**62**) were

attempted employing PIDA in other non nucleophilc solvents (see section 2.12). Polymeric reaction mixtures were obtained from which no compounds could be isolated.

2.23 Employing a carbonyl group as the external nucleophile

Work carried out concurrently in our laboratory[50] employing the methodology established in section 2.2 used a carbonyl group as the nucleophile. It was hoped that cyclisation would occur in the 4 position of 3-substituted phenol (**64**) to give the dione (**65**).



Scheme 24

A single new product was observed to have formed by HPLC with all starting material being consumed using 2eq PIDA. After work up and purifcation, spectral data revealed that the 4,4-dimethoxycyclohexa-2,5-dienone (**66**) had been obtained in poor yield (40%).

2.24 Conclusion

Results indicated that the side chain was not nucleophilic enough or that flexibility in the side chain prevented the molecule adopting the preferred conformation required by cyclisation to proceed. Having attempted to solve the former to no avail, we tried to put the latter idea into practice to see if the desired compounds could be formed.

Chapter 3

Introducing Rigidity into the Nucleophilic Side Chain

3.1 Introduction

The results from chapter 2 showed that oxidation occurred simply and effectively on the various phenols assayed, however the desired chromenones were never formed.

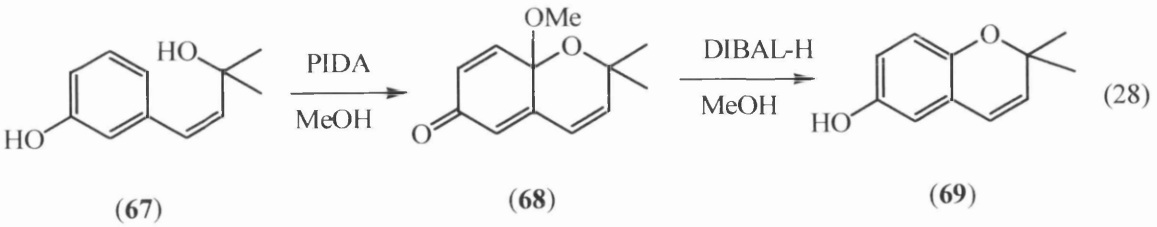
Having attempted unsuccessfully to influence cyclisation by manipulation of the nucleophilicity of the alkene side chain on the chosen phenols, attention was turned to making the side chain more rigid in the hope of aiding cyclisation.

3.2 Increasing the rigdity of the nucleophilic side chain

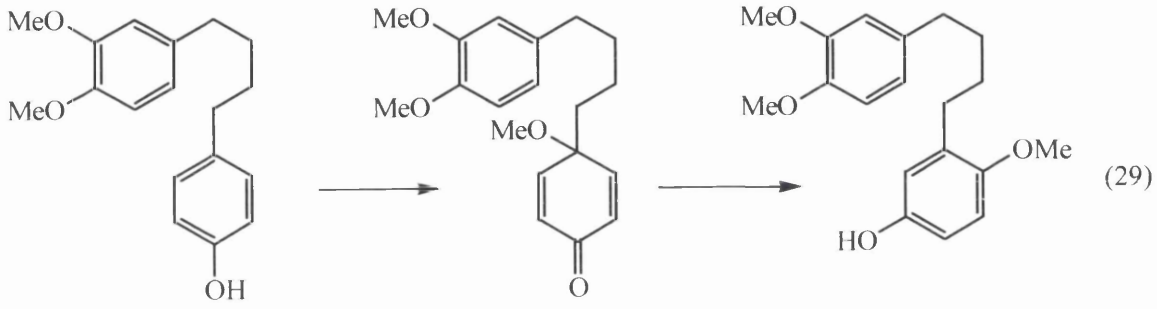
In our laboratories we have seen reactions involving PIDA or PIFA oxidation, (Scheme 10 and eqn. 28),[28,33] where a degree of rigidity in the nucleophilic side chain has aided cyclisation. In Scheme 10, the dibenzylbutyrolactone (**21**), has the two benzyl groups held in a rigid configuration due to the presence of the lactone ring and on oxidation with PIFA it affords either the cyclooctadienes (**21**, **22**) or spirodienone (**23**) depending on the time allowed for the reaction.

Similarly in eqn 28, the nucleophilic side chain on the phenol (**67**) is rigidly held in position by the alkene bond, and on oxidation with PIDA it affords the chromene (**68**) in good yield.

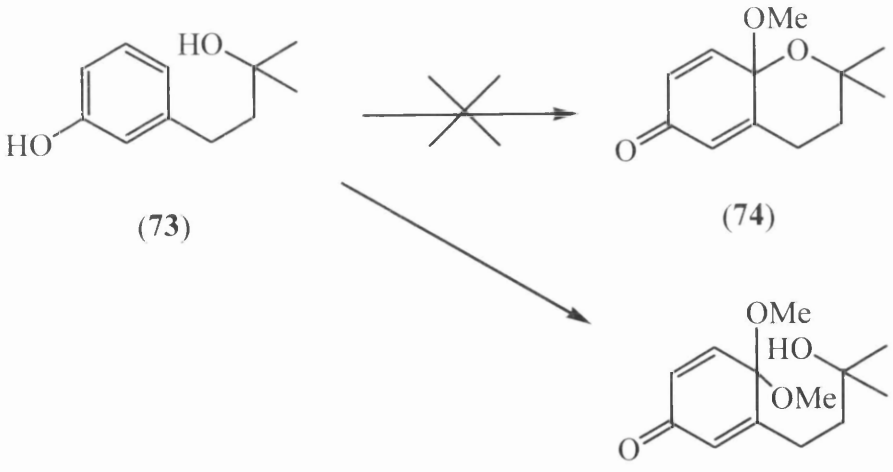
These results provide evidence that some form of rigidity, as well as a stronger nucleophile in eqn 28, are needed for cyclisation to occur. They are in stark contrast to other interesting findings in the same studies (eqn 29) (scheme 25).



(67) (68) (69) (28)



(70) (71) (72) (29)



(73) (74) (75)

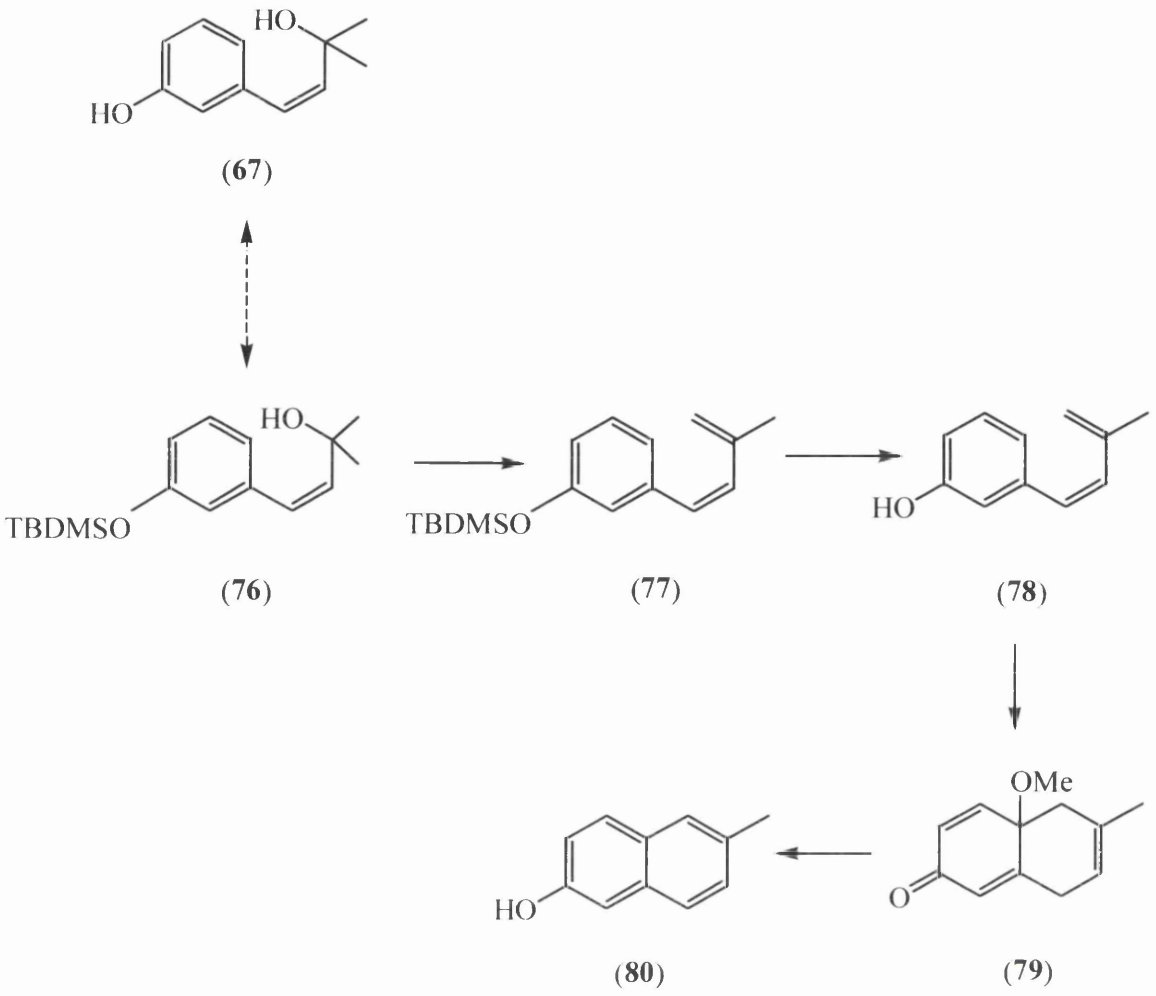
Scheme 25

The reaction in eqn 29 shows that no cyclisation occurs when the diarylbutane (**70**) is treated with PIDA or PIFA. Instead, the 4-methoxycyclohexadienone (**71**) is the sole product of PIDA/PIFA oxidation, in low yield. On treatment with acid, to try to induce cyclisation, the rearranged product (**72**) was the only one to be obtained. In view of the results using dibenzylbutyrolactones discussed earlier, it would appear that a lack of rigidity in the nucleophilic side chain in this reaction has resulted in no cyclised products being formed.

Similarly with Scheme 25, the sole product of the PIDA oxidation on phenol (**73**) was the dimethoxyquinone monoketal (**75**) also in low yield. Attempted acid-catalysed cyclisation of this product yielded no isolatable products. This result suggests that the rigidity of the *cis* alkene, by holding the nucleophilic side chain close enough to the proposed phenoxonium ion site on C-4 of the phenol, is essential for cyclisation.

In concurrent work in our laboratory, the product (**76**) had been synthesised. This was an interesting product as it could be simply converted to the precursor (**77**) by dehydration of the alcohol. Subsequent removal of the *tert*-butyldimethylsilyl group would lead to a new oxidation precursor (**78**).

Although the envisaged end product (**79**) whilst not very interesting, if obtained, would prove the point of rigidity in the nucleophilic side chain (Scheme 26).



Scheme 26

3.3 Preparation of phenol (78)

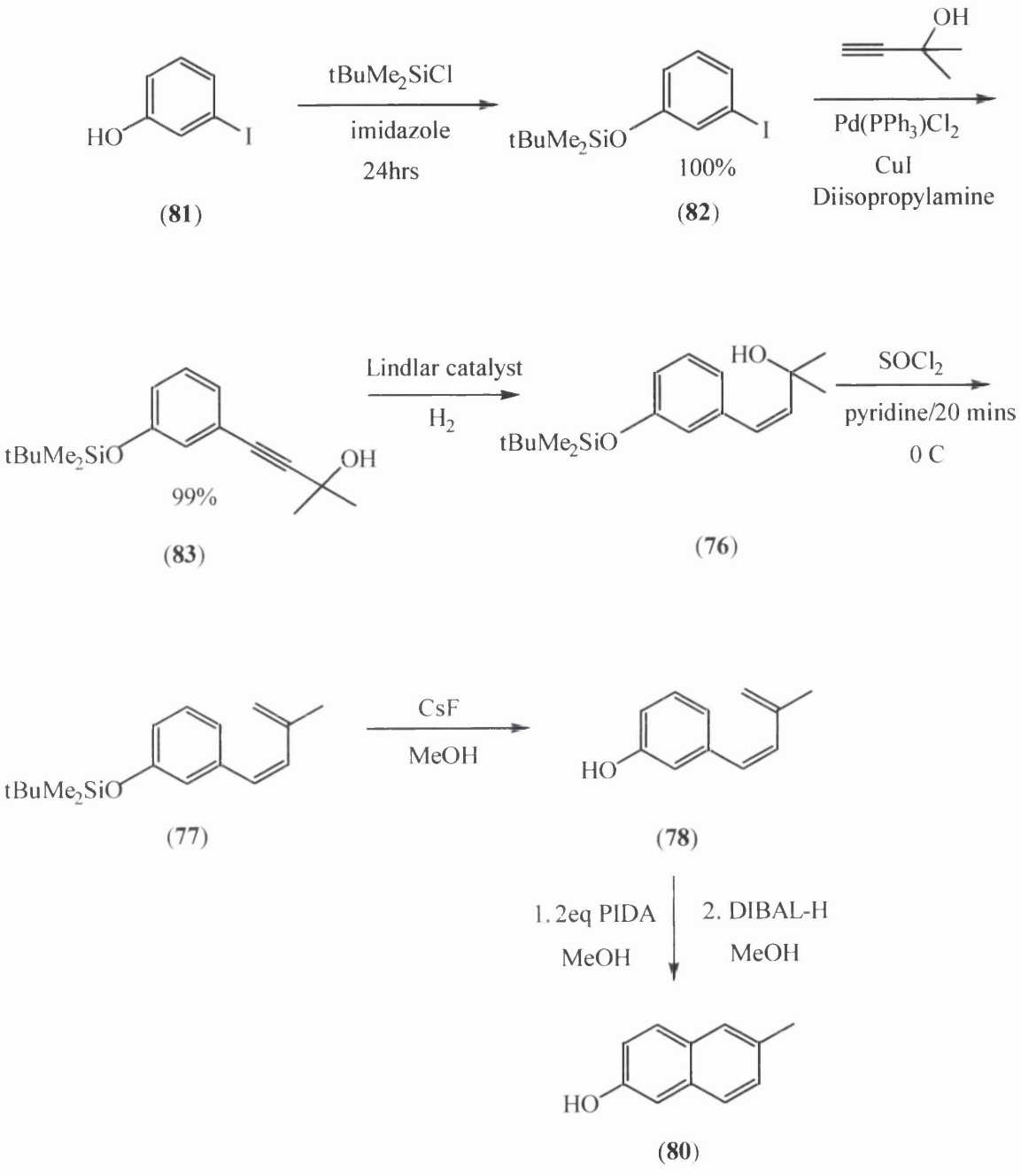
Attempted synthesis of (**78**) was begun, using the method worked out by Smith *et al* [33] in our laboratories, and it seemed sensible to use this already tried and tested approach for our purposes (Scheme 27).

3-Iodophenol (**81**) was quantitatively converted to (**82**) by stirring overnight with *tert*-butyldimethylsilyl chloride, imidazole and dichloromethane. Reaction of (**82**) with 2-methylbut-3-yn-2-ol, a palladium catalyst and CuI in diisopropylamine afforded compound

(**83**) again in quantitative yield. Hydrogenation of (**83**) with Lindlar catalyst gave good yields of (**76**) but only after repeated attempts, possibly caused by the catalyst becoming poisoned by impurities. Over-hydrogenation was also a problem encountered using this procedure with the result that it required careful monitoring. Another method subsequently used to give very good yields of alkene was titanocene dichloride and *iso*-butyl magnesium chloride.[51]

This proved a quick, versatile and fairly high yielding reaction particularly for the alkynes used in later reactions, as hydogenation of these compounds using Lindlar catalyst proved very difficult.

Dehydration of the alcohol (**76**) would hope to give the *cis* diene (**77**) and on obtaining this, subsequent removal of the *tert*-butyldimethylsilyl group using CsF could give us the desired starting phenol (**78**).


HO
I
(81)
tBuMe2SiCl
imidazole
24hrs
tBuMe2SiO
I
100%
(82)
OH
Pd(PPh3)Cl2
CuI
Diisopropylamine
tBuMe2SiO
OH
99%
(83)
Lindlar catalyst
H2
HO
tBuMe2SiO
(76)
SOCl2
pyridine/20 mins
0 C
tBuMe2SiO
(77)
CsF
MeOH
HO
(78)
1. 2eq PIDA
MeOH
2. DIBAL-H
MeOH
HO
(80)

Scheme 27

3.4 Dehydration of the alcohol (76)

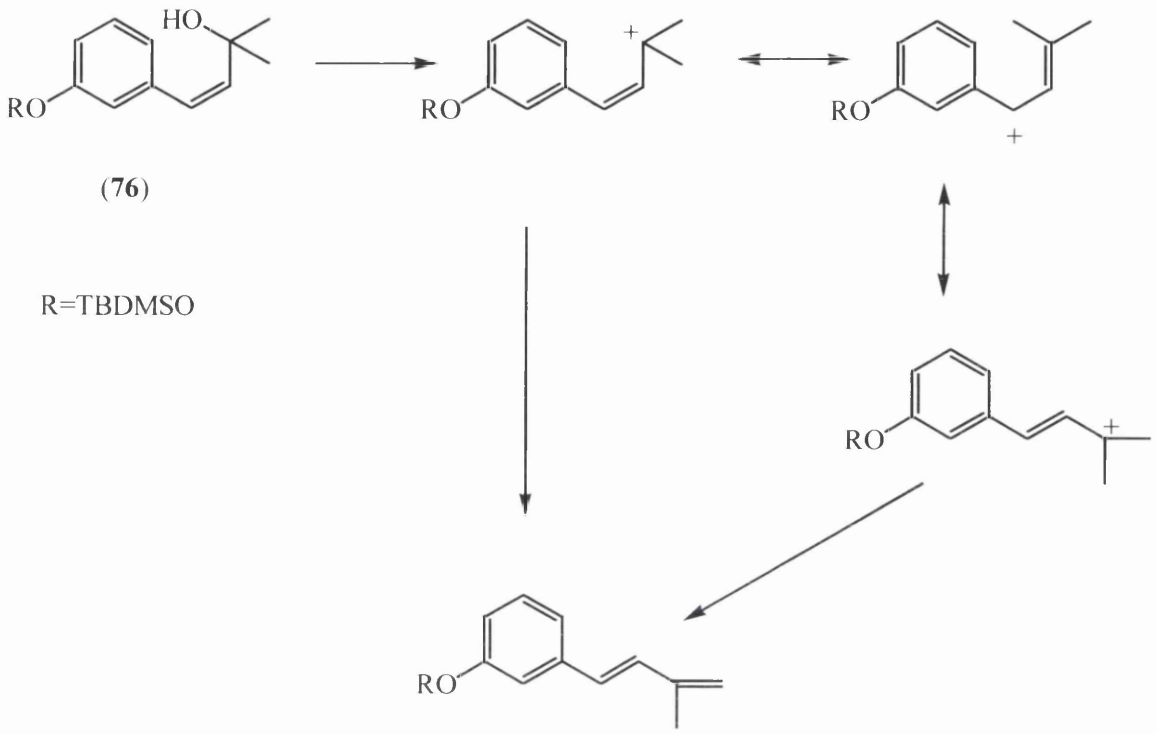
Dehydration of the alcohol (**76**) to obtain the desired diene was attempted in a number of different ways. Those considered were $CuSO_4$/silica gel,[52] *p*-TsOH,[53] thermolysis of xanthate esters[54] and thionyl chloride.[55]

3.4.1 $CuSO_4$/silica gel

Dehydration of the alcohol was attempted using the method employed by Nishiguchi *et al.*[52]. The alkene was obtained, however isomerisation of the allylic cation occurred and the *trans* isomer (**84**) was the sole product of the reaction. Dehydrations using $CuSO_4$ and silica gel produce a carbocation which can delocalise on the allylic side chain and hence the less strained and more energetically stable *trans* product was obtained. Detection of the *trans* isomer was achieved using nmr studies and comparison with calculated chemical shifts.

3.4.2 *p*-TsOH

The dehydration technique employed by Utermoehlen *et al* [53] was also tested at the same time. Like the $CuSO_4$/silica gel method it too produces a carbocation and as a result also gave the *trans* isomer as the sole product (Scheme 28).



(**76**)

R=TBDMSO

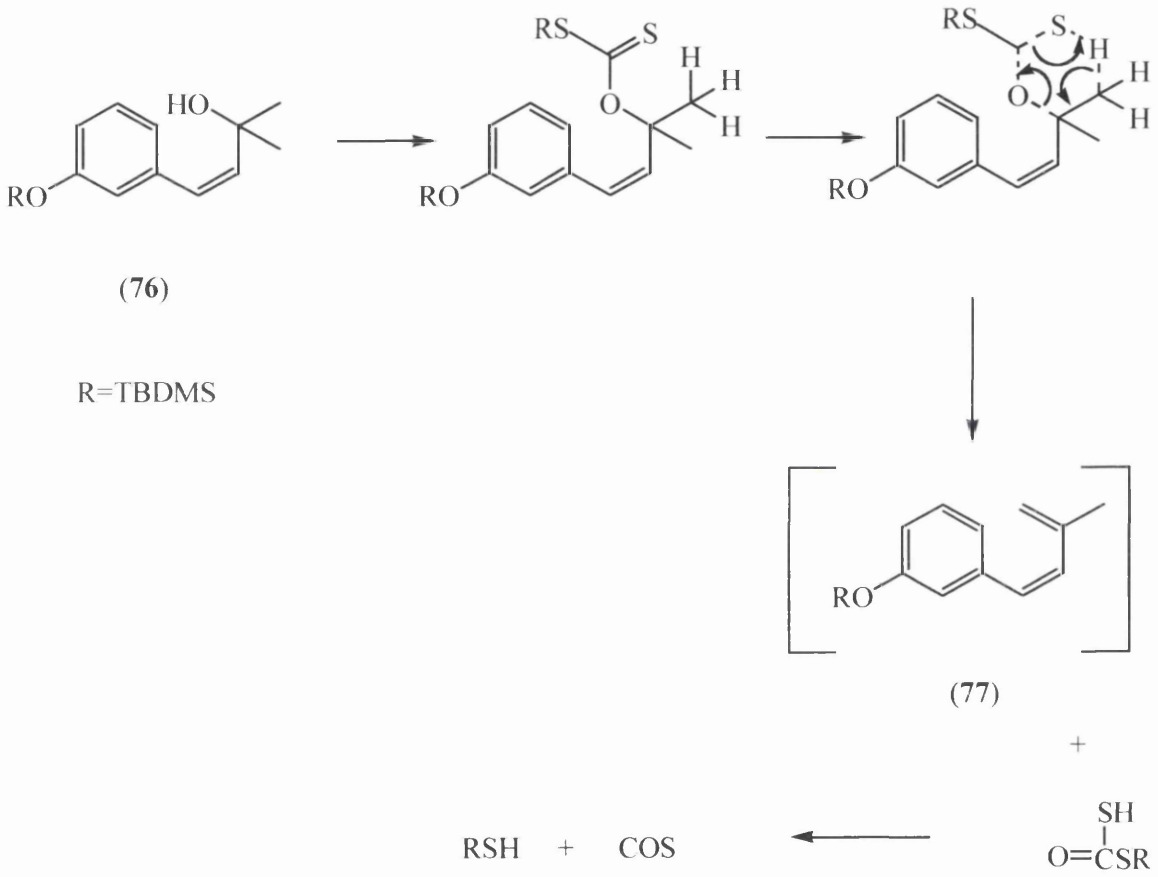
(**84**)

Scheme 28

Xanthate esters and thionyl chloride were used as alternative dehydration methods as their modes of reaction would not generate a positive ion, but rather react *via* a cyclic intermediate and hence keep the *cis* configuration that was required.

3.4.3 Use of Xanthate esters [54] as a dehydrating derivative

The reaction was expected to proceed as in Scheme 29, to give the desired *cis* diene(**78**).



(**76**)

R=TBDMS

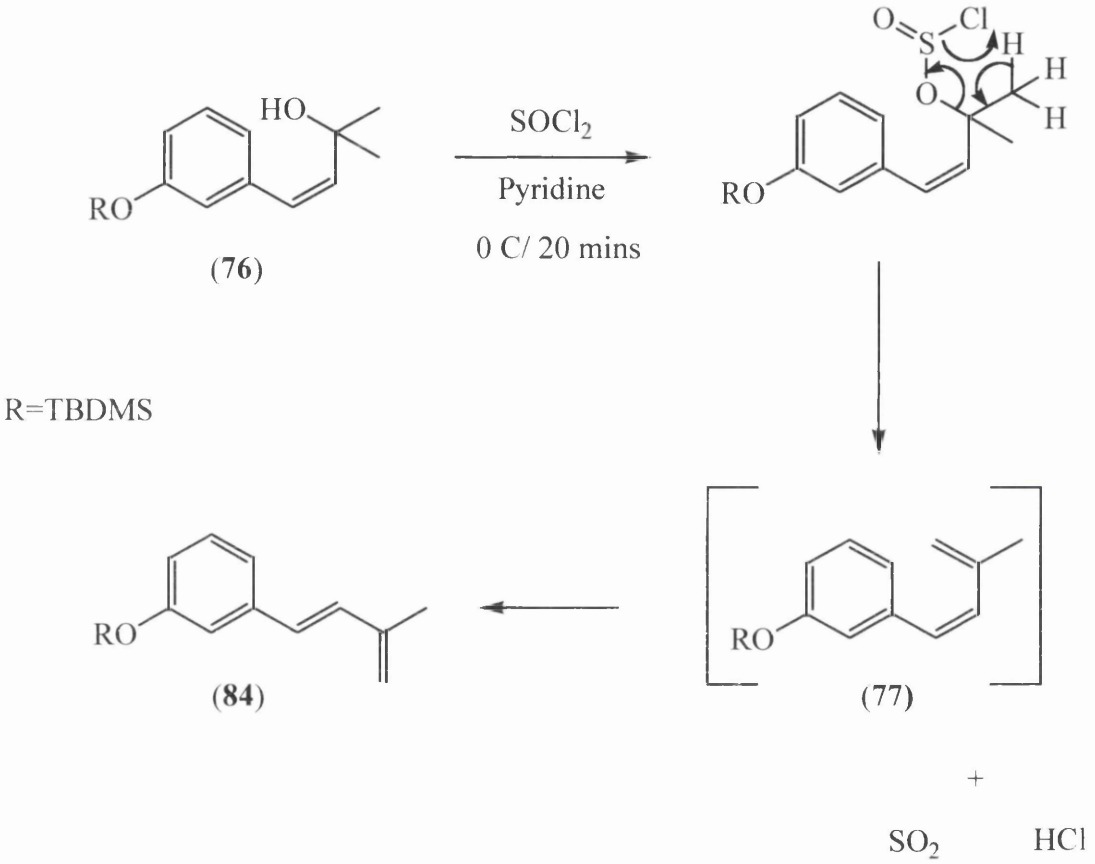
(**77**)

Scheme 29

The proposed product from the xanthate ester reaction (**77**) was never isolated from the product mixture. We were dealing with a tertiary alcohol but no precedent had been found for this reaction (all previous results had been obtained with secondary alcohols only). Our attention then turned to thionyl chloride as a dehydrating reagent, as it too produces a cyclic intermediate on reaction.

3.4.4 Thionyl chloride as a dehydrating reagent[55]

Thionyl chloride in dichloromethane was added by syringe to a mixture of starting material (**76**), pyridine and dichloromethane at 0°C under nitrogen[55]. The reaction was expected to yield the *cis* diene.



Scheme 30

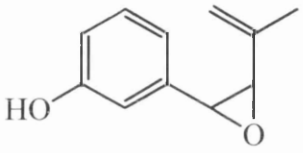
The *cis* isomer (scheme 30, (**77**)) may have been formed along with the trans isomer (**84**) on completion of the reaction. Tlc of the reaction showed 2 products had been formed. Nmr (100 MHz) of the crude product was not convincing so the products were separated quickly by column chromatography. The *trans* product (**84**) was only obtained rendering the product unacceptable for our purposes. The *cis* product may have formed but it was evident

that the *trans* configuration of compound (**84**) was energetically more stable than the *cis* hence it was the only compound isolated.

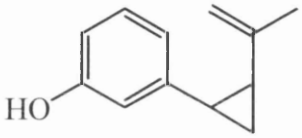
3.5 The use of epoxide rings as a form of rigidity on the nucleophilic side chain

Other forms of rigidity were then considered for the side chain, where the *'cis'* configuration may be obtained.

The two possibilities thought of were epoxides (**85**) and cyclopropanes (**86**) i.e.



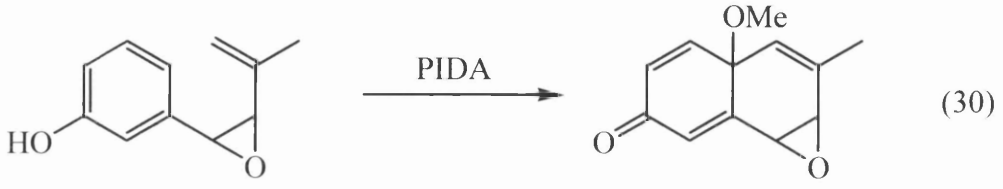
(**85**)



(**86**)

Epoxides were first considered due to the simple nature of the epoxidation.[56,57] Cyclopropanes will be discussed later.

Should the product (**85**) be synthesised and the subsequent PIDA oxidations proceed (eqn 29), this would lead to a large number of possibilities within synthetic organic chemistry. For example, by using asymmetric epoxidation techniques[58], we would be able to synthesise highly fuctionalised end products, to be used as precursors in a variety of different reactions.

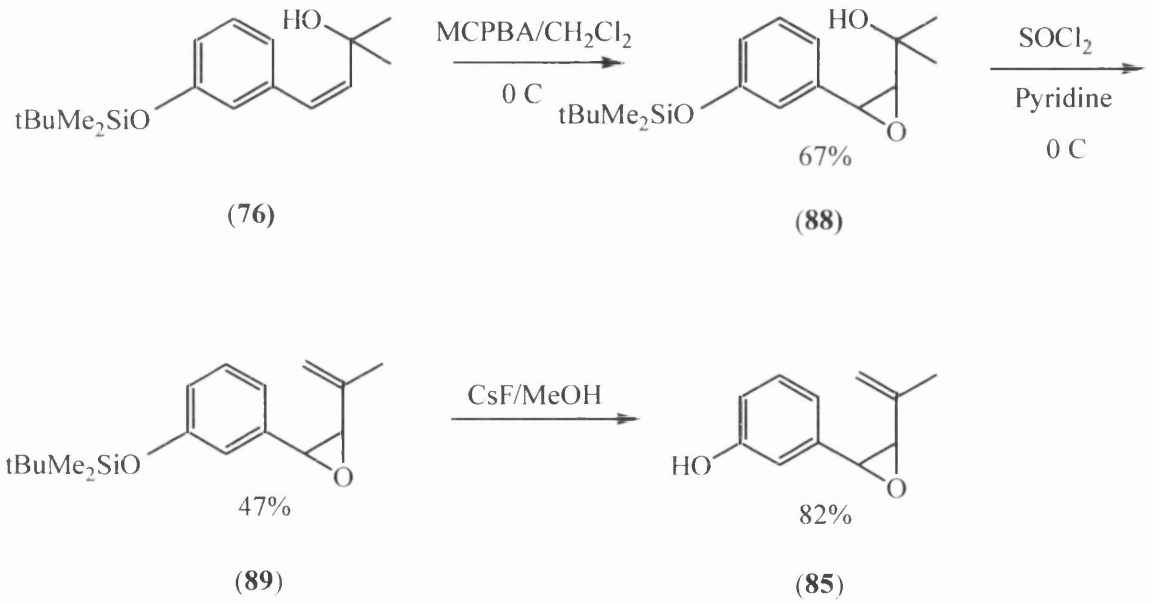


(30)

(**87**)

3.6 Preparation of epoxyphenol (85)

Making use of the methodology that has already been established, alcohol (**76**) was treated with *m*-CPBA in dichloromethane[59] to give, after purification, epoxyalcohol (**88**) in 67% yield. Subsequent treatment of (**88**) with $SOCl_2$ provided us with the desired epoxyalkene (**89**) in 47% yield. Finally, removal of the *t*-butyldimethylsilyl protecting group afforded the desired epoxyphenol (**85**) in 82% yield (Scheme 31).

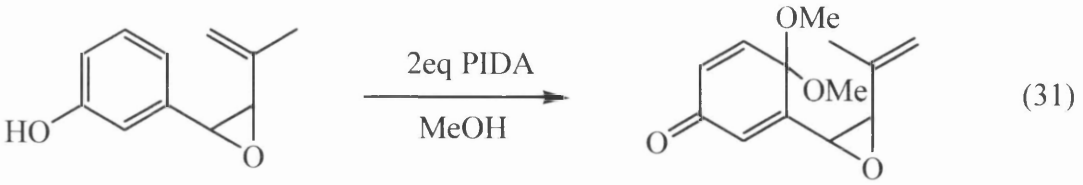


Scheme 31

3.7 PIDA oxidation of epoxyphenol (85)

With the desired phenol (**85**) in hand, PIDA oxidation was attempted using methanol as the solvent medium. On addition of one equivalent of PIDA, a single new peak on the hplc trace was seen as well as starting material. Addition of another equivalent of PIDA gave the new product only on the hplc trace and no starting material. Upon work up and

purification, the product was identified as dimethoxyquinone monoketal (**90**) in 38 % yield (eqn. 31).



(31)

(**90**)

Oxidations were also tried in other solvents such as 2,2,2-trifluoroethanol, MeCN and dichloromethane but gave polymeric products only. Similarly, upon treatment of (**89**) with various acids to try to stimulate cyclisation, and following the reaction by hplc, a large number of products were seen to form however none could be isolated.

3.8 Conclusion

Having managed to achieve our aim of synthesising phenols with the desired rigidity in the nucleophilic side chain, subsequent oxidation of the compound failed to deliver any cyclised products. Further modifications to the starting phenols would be needed, possibly involving a stronger nucleophile than the alkenes that have been previously utilised.

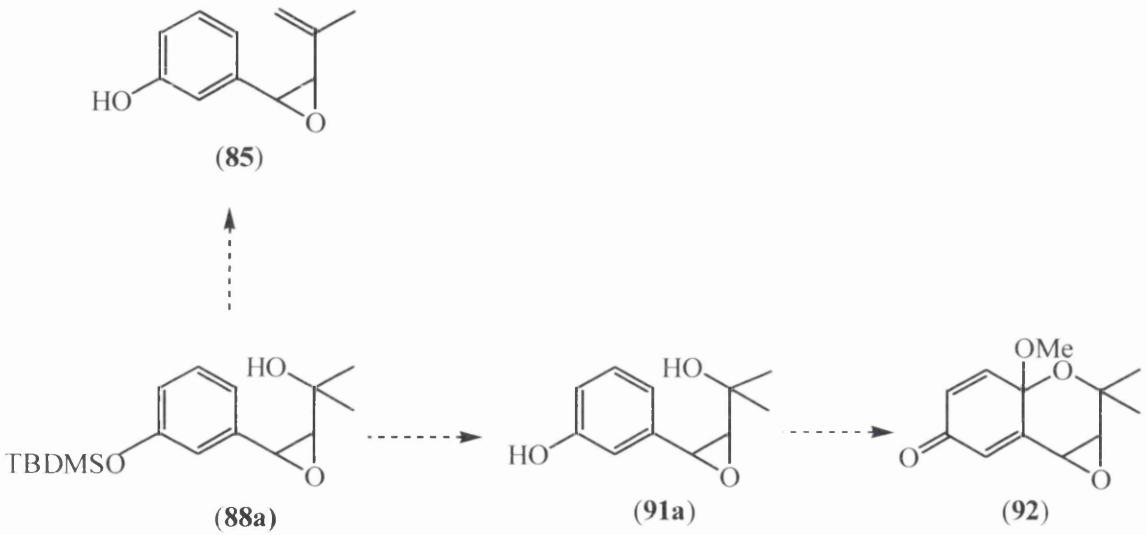
One interesting aspect of the oxidation in section 3.5 was that although the reaction did not produce the desired cyclised product, the epoxide ring was shown to withstand the PIDA oxidation reaction conditions.

Chapter 4

Attempted preparation of Epoxychromanones

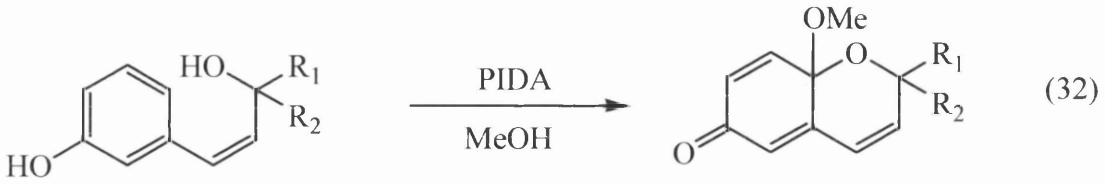
4.1 Introduction

On reflection on the proposed new method to produce compound (**85**) in chapter 3 it was noticed that another interesting precursor (**91a**) could also be made by deprotection of the phenolic group in compound (**88a**) and that this new compound with a greater nucleophilic side chain may then undergo PIDA oxidation (Scheme 32).



Scheme 32

Experiments in our laboratories have already shown that the alkene equivalent (**67a**) of epoxyalcohol (**91a**) could undergo PIDA oxidation to yield the corresponding chromenones[33] (**68a**),(eqn. 31). Other alcohols were also subjected to PIDA oxidation, all resulting in the desired chromenones being formed each time. These alcohols could also be easily converted to epoxyalcohols and subsequent PIDA oxidations could prove interesting.



(32)

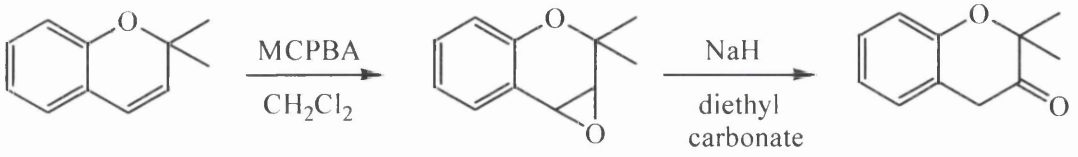
(67a-d) **(68a-d)**

a : R_1, R_2 = Me b : R_1, R_2 = $-(CH_2)_5-$ c : R_1, R_2 = Ph, H d : R_1, R_2 = Ph

On PIDA oxidation, should cyclisation of epoxyalcohol (**91a**) occur, the resultant epoxychromenone (**92**) would be highly functionalised and could therefore provide good building blocks for a variety of other compounds.

4.2 Epoxychromenes

Epoxychromenes have been found to be useful compounds and have been utilised recently as precursors for a variety of different heterocycles and pharmacological compounds. i.e.

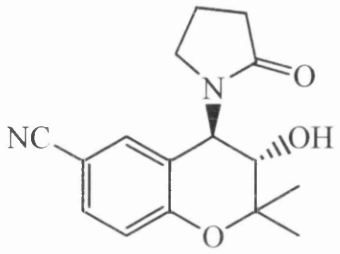


(33)

Much work involving epoxychromenes has been directed towards antihypertensive activity.

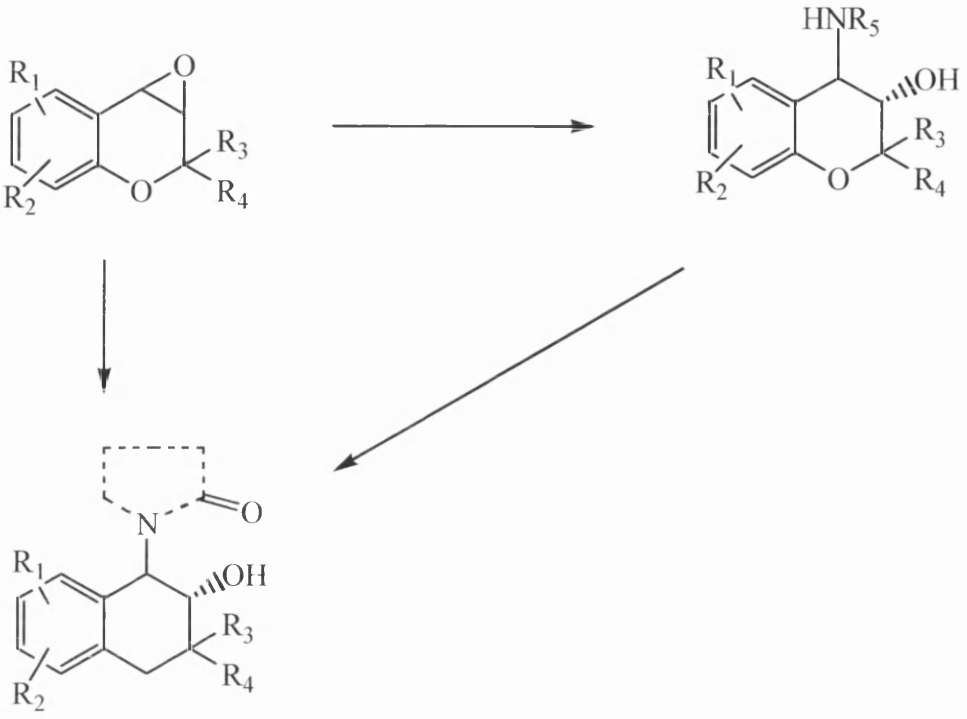
Sodium channel blockers have been used for many years as local anaesthetics and antiarrhythmics. Subsequently calcium channel blockers underwent a vigorous development resulting in a number of drugs that are now widely used in a range of indications. There is now a growing interest in the therapeutic potential of substances that modulate potassium

channels. The new drugs have been shown to hyperpolarise the membrane potential of vascular smooth muscle cells via enhanced efflux of potassium ions through ATP-sensitive channels.[63] The net effect of this process is to relax blood vessels and reduce blood pressure. Cromakalim (**93**), a potent antihypertensive reagent, has been used as a template for many benzopyran potassium channel activators, and much research has concentrated on finding replacements for the 6-cyano substituent. Other research has been directed towards replacing the 4-(2-oxopyrrolidine-1-yl) group .[64,65]



(**93**)

Subsequent synthesis of a series of novel 4-(cyclo amido) -2H-1-benzopyran-3-ols has been achieved.[66] The key step in the preparation of this class of compounds was found to be the action of a cyclic amido anion on an appropriate epoxide. Treatment of the corresponding epoxides with cyclic amide and 1 equivalent of NaH furnished the majority of the desired compounds (**94**) (Scheme 33).

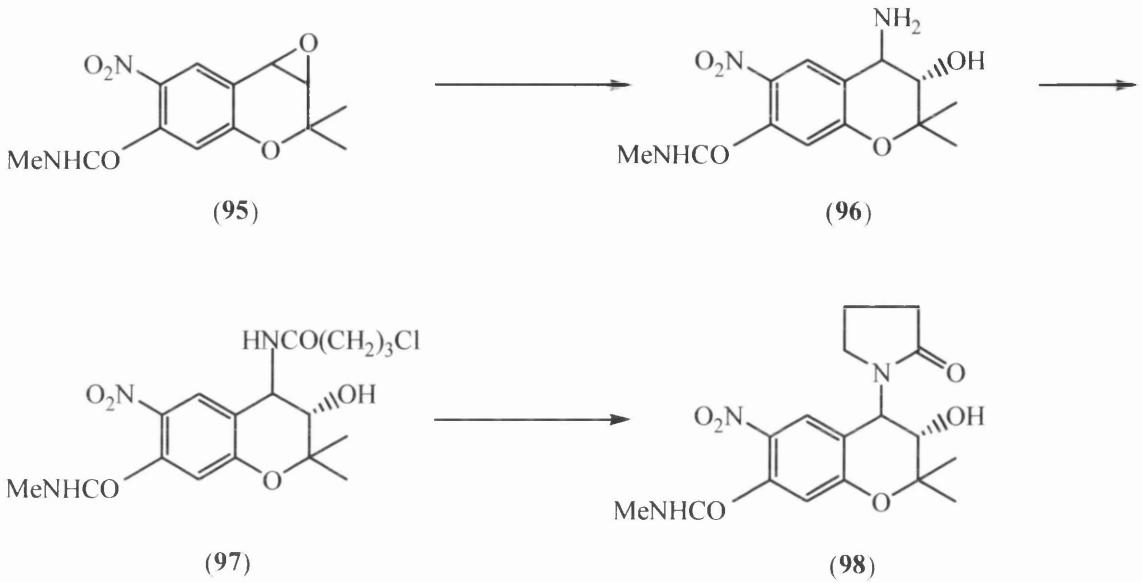


(**94**)

Scheme 33

Other possible antihypertensive compounds were also synthesised from epoxides by reaction with ethyl 4-amino butyrate.

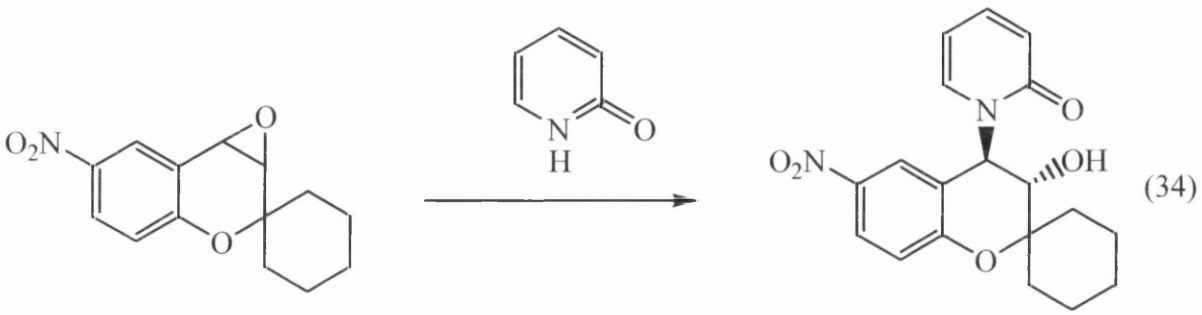
The 6,7 disubstituted compound (**98**), (Scheme 34) was not conveniently prepared this way, so the epoxide (**95**) was converted to the 4-amino compound (**96**) and this was treated with chlorobutyryl chloride to give (**97**) which was intramolecularly cyclised with NaH to give (**98**).[67]



Scheme 34

Other more complicated benzopyran-3-ols could also be synthesised from their equivalent epoxy compounds.

When the epoxides are reacted with 2-pyridones in pyridine and alcohol, the main products are the (+)-*trans*-3,4-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyran-3-ols frequently obtained in pure crystalline form (eqn.34). The same studies have shown that the epoxides can not only react with 2-pyridones, but 4-pyridones, pyridazinones, pyrimidones and pyrazinones all in pyridine/ethanol mixtures.

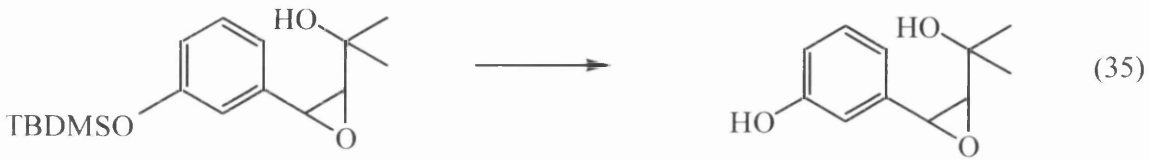


(34)

Epoxychromenes have also been used to make chiral amino acids. Ammonolysis of non racemic epoxides has lead to the formation of these compounds which can then be used for the preparation of individual enantiomers.

4.3 Preparation of epoxy alcohol (91a)

Deprotection of alcohol (**88a**) using CsF as in section 2.4, gave phenol (**91a**) in quantitative yield, which was simply purified by column chromatography (eqn 35).



(35)

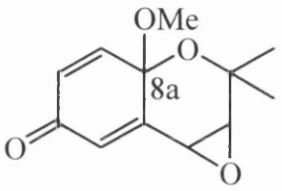
(**88a**) (**91b**)

4.4 PIDA oxidation of epoxy alcohol (91)

With the epoxy alcohlol (**91a**) now at hand, oxidation was attempted in the usual manner using methanol as the solvent medium and hplc to follow the reaction.

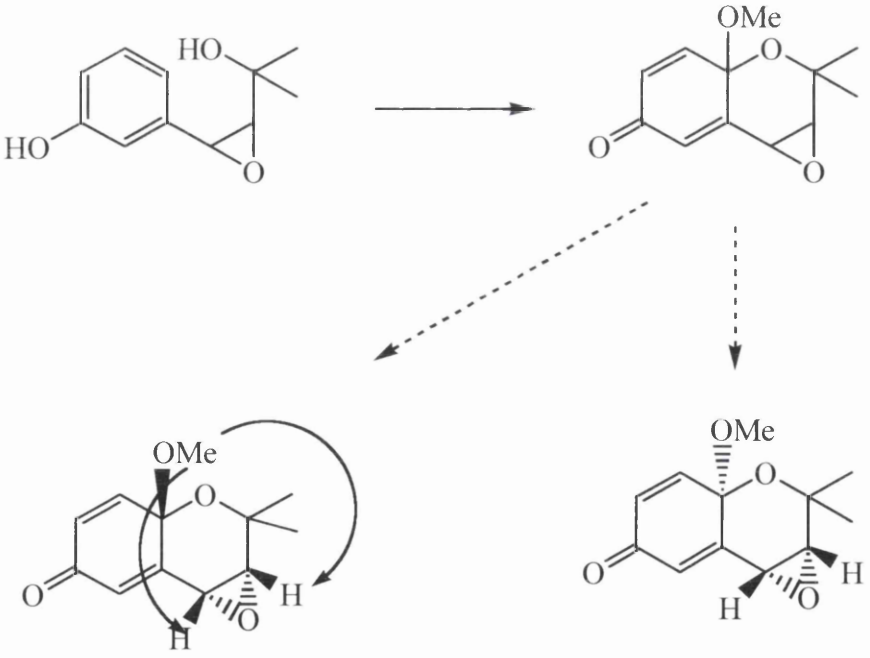
Upon addition of one equivalent of PIDA, the hplc trace of the reaction mixture showed two new product peaks had formed and that starting material was still present. Addition of another equivalent of PIDA showed only the two new product peaks. The reaction mixture was quenched and after work-up gave a yellow/orange oil.

Analysis of this oil using nmr showed that two isomers of epoxychromenone (**92**) had indeed been formed in moderate yield (58%) in a 4:1 ratio caused by the introduction of the new chiral centre at position C-8a.



(**92**)

The diastereomeric chromene derivatives were separated using column chromatography and examination of the NOESY spectra showed the isomers to be (**92a**) 37% and (**92b**) 10%. The major isomer was shown to be (**92a**) in which the methoxyl group that had been introduced at C-8a was *trans* to the epoxide ring, hence strong NOE interactions were seen between the methine hydrogens of the oxirane and the hydrogens of the methoxyl group (as shown by the curved arrows on (**92a**)).



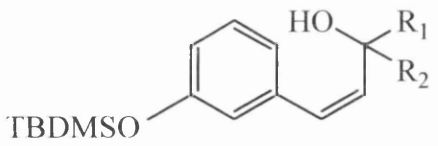
(**92a**) (**92b**)

Scheme 35

No such interactions were seen for compound (**92b**), the minor isomer. One would expect this result regarding the diastereomeric ratio of products due to steric factors, in that having the two bulky oxirane and methoxyl groups as far apart as possible would minimise steric hindrance and reduce electron repulsion between the two groups. Hence, the *trans* isomer would be expected to predominate.

4.5 Other epoxychromene possibilities

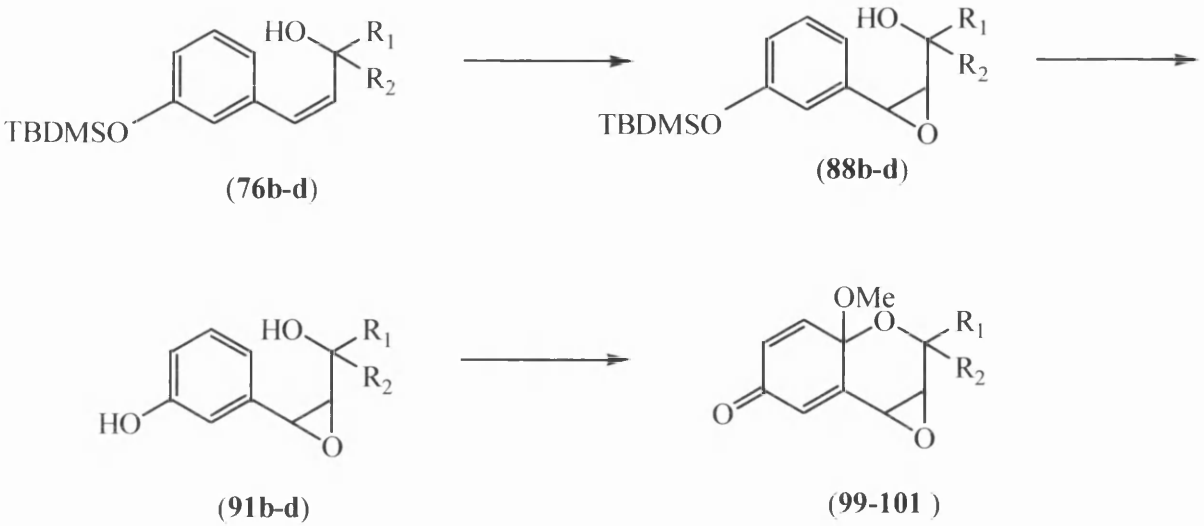
Other similar compounds to (**91a**) were then put to the test. Concurrent work being carried out in our laboratories had produced compounds (**76b-d**) which on deprotection of the *tert*-butyldimethylsilyl group had produced (**67b-d**) .



(**76b-d**)

b : $R_1, R_2 = -(CH_2)_5-$ c : $R_1, R_2 =$ Ph, H d : $R_1, R_2 =$ Ph

Could we then utilise these ready made compounds and envisage them undergoing similar reactions to (**88a**) to give the corresponding epoxychromenones? (Scheme 36).



Scheme 36

4.6 Preparation of epoxy alcohols (91b), (91c),(91d)

Compounds (**88b,c,d**) were prepared by dissolving (**76b,c,d**), (already prepared during concurrent work in our laboratory[33]), in dry dichloromethane and one equivalent of *m*-chloroperbenzoic acid in dry dichloromethane was added *via* a dry nitrogen flushed double ended needle at 0°C. After 2 hours the *m*-chlorobenzoic acid was filtered off and the filtrate concentrated down and purified by column chromatogaraphy to yield (**88b**) (59%) as a colourless oil, (**88c**) (57%) as a yellow oil and (**88d**)(49%) as a yellow oil.

4.7 Deprotection of the TBDMS derivatives to give phenols (91b,c and d)

Simple deprotection of the *tert*-butyldimethylsilyl protecting group as in section 3.6, was effected using CsF to give the corresponding phenols (**91b**) (95%), (**91c**) (98%) and (**91d**) (75%) in quantitative or good yields.

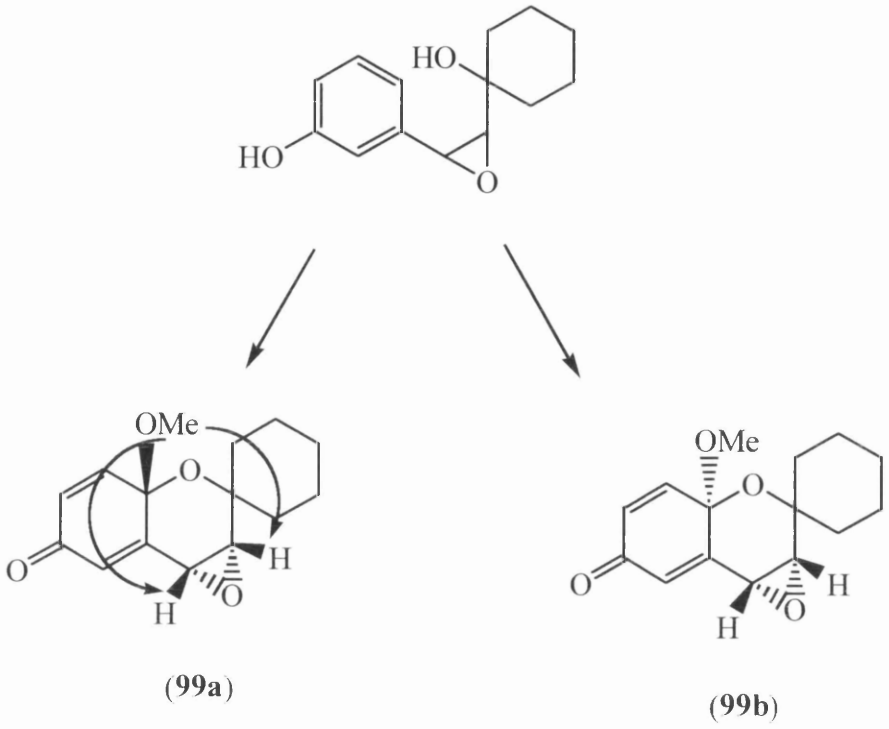
4.8 PIDA oxidation of alcohol (91b)

After simple preparation of alcohol (**91b**) by deprotection using CsF, PIDA oxidation was carried out in the usual manner.

The reaction appeared to mirror the earlier example, as again hplc showed on addition of one equivalent of PIDA the formation of two new product peaks and starting material. Hplc showed on the addition of the second equivalent of PIDA, two new peaks and no starting material.

After work-up and purification, a yellow oil , 0.551g (65%) was obtained which by nmr showed the two diastereomeric isomers (**99a**) and (**99b**) had been formed in a 4.7:1 ratio. The major isomer was shown by NOESY spectroscopy to be that where the newly introduced methoxyl group at the C-8a position was *trans* to the oxirane ring as strong NOE interactions were observed between the methine hydrogens and those of the methoxyl group (**99a**), Scheme 37.

The minor isomer again showed no such interactions, suggesting a *cis* configuration between oxirane ring and methoxyl group (**99b**).



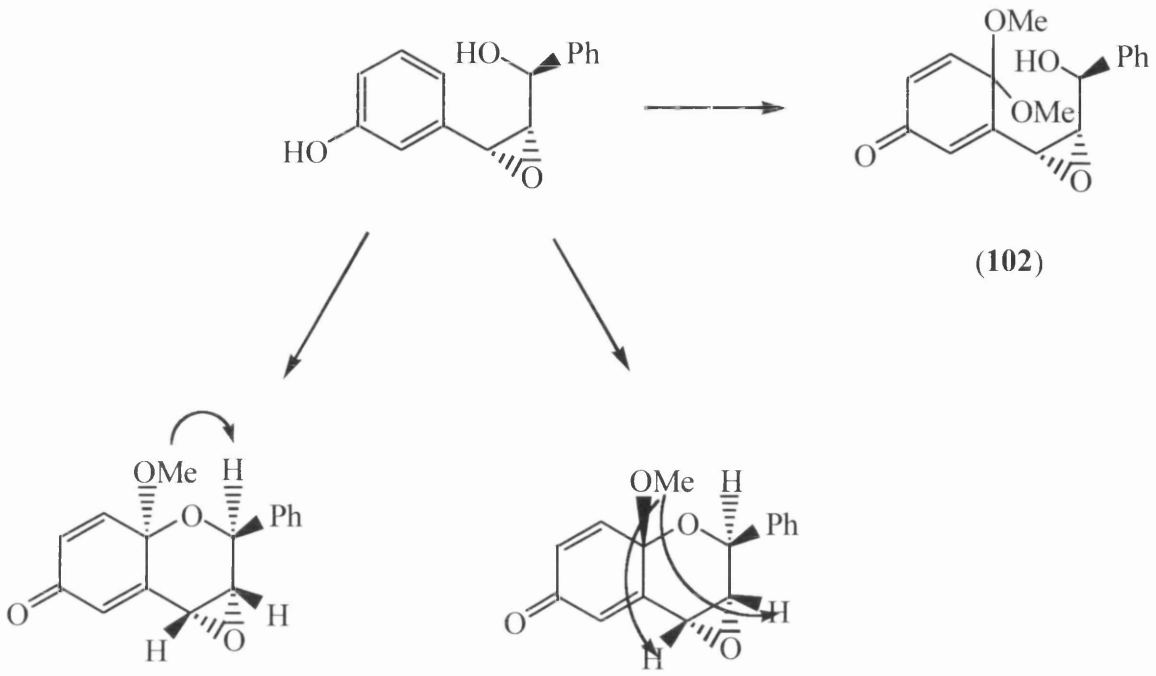
(**99a**) (**99b**)

Scheme 37

4.9 PIDA oxidation of alcohol (91c)

Racemic phenol (**91c**) was then subjected to PIDA oxidation and again was followed using hplc. It was noted on addition of one equivalent of PIDA, that there were now three new product peaks as well as one for the starting material. Another equivalent of PIDA saw the starting material disappear as was to be expected and the three new peaks become enhanced.

Both ^{1}H and ^{13}C nmr were used to determine the products which suggested that two chromene derivatives had been formed in a 3:2 ratio (**100a** and **100b**) and that uncyclised quinone monoketal (**102**) had also been formed . Again the NOESY spectra of the two cyclised products was used to determine their configuration, scheme 38.



(**102**)

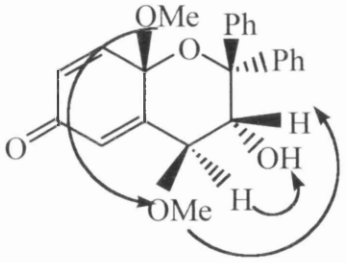
(**100a**)

(**100b**)

The major isomer was given the configuration (**100a**), as clear interaction (curved arrows in scheme 38) was seen between the hydrogens of the methoxyl group and the methine proton at C-2. No interaction was seen between these signals and the methine protons at C-3 and C-4. The structure (**100b**) was given to the minor isomer as in contrast to that for (**100a**), a strong NOE interaction was seen between the methoxyl group and H-4 and another weaker signal between the methoxyl hydrogens and H-3. No interaction was seen between H-2 and the methoxyl protons or the methine protons at C-3 and C-4. It was through working backwards from these findings that the stereochemistry of precursor (**91c**) was assigned as the *erythro* configuration. The data obtained for quinone monoketal (**102**) was in line with that obtained for similar compounds in chapter 2.

4.10 PIDA oxidation of phenol (91d)

When phenol (**91d**) was subjected to PIDA oxidation a single new peak appeared on the hplc trace, along with that of starting material. Addition of another equivalent of PIDA gave only the single new peak. Work-up and purification of the new compound gave a yellow oil. Having checked the spectral data for this compound , it was clear that it was not the expected cyclised epoxide since there were two methoxyl groups present, not one as was to be expected. One of the methoxyl groups was distinguished by the fact it gave a signal at δ2.64 in the ^{1}H nmr spectrum which suggested that this particular methoxyl group was held in close proximity to one of the phenyl rings. The conclusion drawn from the data obtained was that it was in fact a cyclised product whereby the oxirane ring had opened due to attack from methanol. This compound was subjected to NOESY spectroscopy and the isomeric configuration below was assigned to this highly functionalised new product (**101**).



(**101**)

Strong NOE interaction between the two methoxyl groups was observed and also between the methoxyl group at low field and H-3, and the O-H group and H-4 (all shown by curved arrows). No interactions however were seen between the high field methoxyl group and H-4, or between H-3 and H-4, as would be expected.

4.11 Conclusion

The results showed conclusively that the oxirane ring provided enough rigidity on the side chain for the intramolecular reaction to occur. They also showed that the oxirane ring stood up to the PIDA oxidation process apart from oxidation of compound (**102**) which appears to be formed due to steric factors caused by the strain of five rings in a compact molecule as opposed to chemical instability of the oxirane ring to PIDA. Finally there is also the prospect of using homochiral precursors to possibly stereoselectively synthesise highly functionalised homochiral chromenone derivatives.

Chapter 5

Miscellaneous

5.1 Future work

Unfortunately due to time constraints our encouraging work in chapter 4 could not be capitalised on. It was hoped to reduce the chromenones to the corresponding chromenes[68,69] (see scheme 26 for a possible routing).

Another option open for new work would be to exploit the fact that epoxidation occurs readily on the alkenes (**76a-d**) and the subsequent compounds hold up to the PIDA oxidation, even in the presence of the acetic acid produced in the PIDA oxidation, by trying to produce chiral epoxides. The benefits of this option would be to create building blocks to produce very highly fuctionalised heterocyclic compounds.

One final thought would be to replace the epoxide ring on our compounds with other fuctional groups that will hold the nucleophilic side chain rigid. One option would be to replace the epoxide ring with a cyclopropane ring. A number of unsuccessful attempts at cyclopropanations[70,71,72] on (**76a**) were tried but no compounds were formed and we could not examine this option further.

Again, this opens up the possibilities of creating many other compounds through PIDA oxidation.

Chapter 6

Experimental

6.1 Experimental

All NMR spectra were recorded on a Bruker spectrometer at 100MHz, 250MHz and 400MHz (proton) and 62.9MHz (carbon). All spectra used tetramethylsilane as the internal standard, and were run in deuterated chloroform, unless stated otherwise. All mass spectra were recorded on a VG-12-250 low resolution quadrupole mass spectrometer, while a ZAB-E, high resolution, double focussing mass spectrometer was used for accurate mass measurements. Infra-red spectra were recorded as films on NaCl discs using a Perkin-Elmer Fourier transform 1725X spectrometer and ultra-violet spectra were recorded on a Philips PU8720 scanning spectrometer. Melting points obtained were recorded on an Electrothermal 9100 melting point apparatus, and are uncorrected.

Thin layer chromatography was carried out on Merck 5785 Kieselgel $60F_{254}$ fluorescent plates. Analytical hplc was carried out on a Milton Roy system using a 3100 SpectroMonitor, 3000 ConstaMetric pump and CI-4100 integrator. Flash column chromatography was performed with silica gel (Fisons Matrex 60, 35-70 micron).

6.2 Reagents

All reactions were carried out using purified anhydrous reagents. Those carried out under nitrogen refer to 'white spot' nitrogen which was dried by bubbling through concentrated sulphuric acid and then passing through calcium chloride granules.

Both diethyl ether and dichloromethane were dried by passing down an alumina column and distilling from calcium hydride. Ethyl acetate was dried over potassium carbonate and distilled from calcium hydride. Tetrahydrofuran was passed down a dry alumina column and distilled from sodium metal and benzophenone. The acetonitrile used for

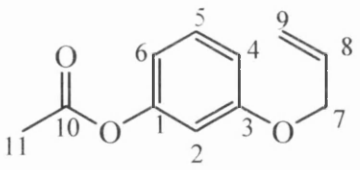
reactions was that supplied by BDH as hplc grade. Methanol was obtained dry by treating with magnesium activated with iodine followed by reflux and then distillation.

6.3 Experimental procedures.

All glassware was dried at 120°C (for at least four hours), assembled hot and cooled under a stream of nitrogen. Low temperature baths were prepared by making a slurry of solid carbon dioxide with acetone (-78°C).

n.b. please note that the numbering of hydrogen and carbon atoms in the experimental is for ease of identification purposes only and is not reflective of the numbering system when naming compounds.

6.4 Preparation of 3-allyloxyphenylacetate (32a)

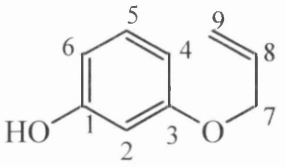


To a dry two necked round bottomed flask (100ml) containing a magnetic follower was added resorcinol monoacetate (5.073g, 33.0 x 10^{-3} mol), potassium carbonate (4.673g,33.0 x 10^{-3} mol) and dry, distilled acetone (20cm^3). Allyl bromide (2.8ml, 33.0 x 10^{-3} mol) was added to the mixture via a syringe whilst stirring. The reaction was then allowed to reflux for 5 hours in an oil bath. Upon cooling, the reaction was washed with water (3x50ml). The combined aqueous layers were then extracted using diethyl ether

all of the organic layers were washed with 2M NaOH solution. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography on neutral silica with CH_2Cl_2, to give (**32a**), (4.942g , 25.7 x 10^{-3} mol , 78%) as a pale yellow oil. (lit. ref. [73]).

Observed mass was 192.2144. Calc. mass of $C_{11}H_{12}O_3$ is 192.2144.δ_H ppm: 2.28 (3H,s, H-11), 4.51 (2H, dt, J=5.3Hz and J=1.5Hz, H-7), 5.27 (1H, ddt, J=8.9Hz J=1.5Hz and J=1.3Hz, H-9), 5.40 (1H, ddt, J=17.2Hz J=1.6Hz and J=1.3Hz, H-9), 6.00 (1H, m, H-8), 6.67 (2H, m, H-2 and H-4 or 6), 6.78 (1H, m, H-4 or H-6), 7.26 (1H, t, J=8.1Hz, H-5). δ_c 21.14 (C-11), 68.94 (C-7), 108.43 (C-2), 112.34 (C-4), 113.93 (C-6), 117.82 (C-9), 129.79 (C-5), 132.90 (C-8), 151.59 (C-1), 159.45 (C-3), 169.35 (C-10) : m/z (CI), 210 (100) , 192 (47), 150 (38), 135(2), 122(8).ν_{max} (cm^{-1}):3082, 3023, 2986, 2925 (C-H) , 1766 (C=O) λ_{max} (MeOH) 232.3nm (ε=5560), 272.5nm (ε=4400), 277.5nm (ε=3880)

6.5 Preparation of 3-allyloxyphenol (24)

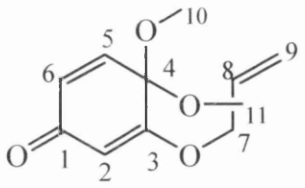


To a dry round bottomed flask (50ml) containing a magnetic follower was added (**32**), (0.505g, 2.6 x 10^{-3}mol) and 2M NaOH solution ($20cm^3$). The flask was fitted with a reflux condenser and the the reaction was allowed to reflux for 1 hour in an oil bath. The reaction was then allowed to cool in an ice bath before 2M H_2SO_4 was added whilst stirring until the pH of the solution had reached 2. The product was then extracted using chloroform

(3x30ml) and these combined extracts were washed with saturated Na_2CO3 solution to remove any acid salts still present. The chloroform layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was separated by flash column chromatography on neutral silica with CH_2Cl_2 to give (**24**) (0.319g, 2.13 x 10^{-3} mol, 82%), as a pale yellow oil. (lit. ref. [74] n.m.r.).

Observed mass was 150.1772. Calc. mass of $C_9H_{10}O_2$ is 150.1772. δ_H ppm: 4.48 (2H, dt, J=5.3Hz, J=1.4Hz, H-7), 5.27 (1H, ddt, J=10.5Hz, J=1.4 and J=1.4Hz, H-9), 5.38 (1H, ddt, J=17.2Hz, J=1.5Hz and J=1.4Hz, H-9), 5.83 (1H,s, OH), 6.02 (1H, ddt, J=17.2Hz, J=10.6Hz and J=5.3Hz, H-8), 6.44 (2H, m, H-2 and H-4 or H-6), 6.49 (1H, m, H-4 or 6), 7.11 (1H, t, J=8.5Hz, H-5) : δ_C ppm : 68.90 (C-7), 102.3 (C-2), 107.19 (C-6), 108.31 (C-4), 117.91 (C-9), 130.45 (C-8), 133.06 (C-5), 156.68 (C-3), 159.82 (C-1) : m/z (EI) 150 (100), 133 (11), 121 (11), 107 (23):ν_{max} (cm^{-1}) 3384 (O-H), λ_{max} (MeOH) 282.0nm (ε=1425), 275.0nm (ε=1687), 229.4nm (ε=2858), 227.5nm (ε=2328).

6.6 Preparation of 3-allyloxy-4,4-dimethoxycyclohexa-2,5-dienone (35)

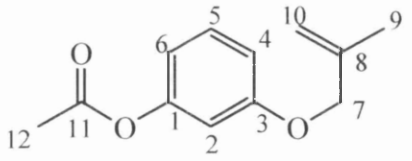


To a dry nitrogen flushed round bottomed flask (100ml), fitted with a septum and containing a magnetic follower was added (**24**), (0.520g, 0.0034 x 10^{-3} mol) in dry methanol (15ml) and PIDA (2.280g, 0.0069 x 10^{-3} mol) in dry methanol (15ml) with good stirring. The solution was stirred for 45 mins before addition of anhydrous K_2CO_3 (0.4g) to remove acetic acid. The reaction mixture was filtered, concentrated under vacuum and the product was

immediately separated by flash column chromatography using CH_2Cl_2 as eluent, giving **(35)** (0.239g, 1.14 x 10^{-3} mol, 33%) as a yellow oil.

Observed mass was 210.2297. Calc. mass of $C_{11}H_{14}O_4$ is 210.2297. δ_H ppm : 3.35 (6H, s, H-10 and 11), 4.54 (2H, dt, J=5.6Hz, J= 1.3Hz, H-7), 5.37 (1H, ddt, J=10.5Hz, J=1.3Hz and J=1.2Hz, H-9), 5.46 (1H,ddt, J=17.2Hz, J=1.3Hz and J=1.2Hz, H-9), 5.64 (1H, d, J=1.9Hz,H-2), 6.00 (1H, m, H-8), 6.31 (1H, dd, J=10.3Hz, J=1.9Hz, H-6), 6.59 (1H, d, J=10.3Hz, H-5) δ_C ppm : 51.44 (C-10 and C-11), 69.73 (C-7), 94.07 (C-2), 104.99 (C-4), 119.66 (C-9), 130.84 (C-6), 131.05 (C-8), 140.68 (C-5) , 167.99 (C-3), 186.26 (C-1): m/z (EI) 210 (100),179 (65), 169 (62),148 (80), 138 (27) :ν_{max} (cm^{-1}) 3019, 2940, 2836 (C-H), 1671 (C=O), 1604 (C=C): λ_{max} : 222.1nm (ε=6720), 248nm (ε=7700)

6.7 Preparation of 3-(2-methyl-allyloxy)-phenylacetate (32b)

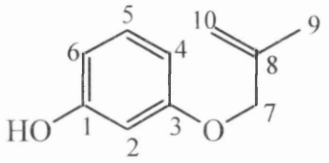


To a dry two necked round bottomed flask (100ml) containing a magnetic follower was added resorcinol monoacetate (5.000g, 33.0 x 10^{-3} mol), potassium carbonate (4.673g, 33.0 x 10^{-3} mol), KI (5.478g, 33.0 x 10^{-3} mol) and dry, distilled acetone (20cm^3). 3-chloro-2-methyl propene (3.25ml, 33.0 x 10^{-3} mol) was added to the mixture via a syringe whilst stirring. The reaction was then allowed to reflux for 5 hours in an oil bath. Upon cooling, the reaction was washed with water (3x50ml). The combined aqueous layers were then extracted using diethyl ether (3x30ml) and all of the organic layers were washed with 2M NaOH solution. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to

dryness. The residue was purified by flash column chromatography on neutral silica with CH_2Cl_2 to give 3-(2-methylallyloxy)-phenylacetate (**32b**) (8.565g, 41.57 x 10^{-3} mol, 63%) as a pale yellow oil. (lit. ref.[75]).

Calc. mass of $C_{12}H_{14}O_3$ is 206.2413. δ_H ppm: 1.81 (3H, s, H-9), 2.27 (3H, s, H-12), 4.40 (2H, s, H-7), 4.98 (1H, d, J=0.6Hz, H-10), 5.00 (1H, d, J=0.6Hz, H-10), 6.60 (2H, m, H-2 and H-4 or H-6), 6.73 (1H, m, H-4 or H-6), 7.19 (1H, t, J=7.8Hz, H-5). δ_C ppm: 19.38 (C-9), 21.12 (C-12), 71.87 (C-7), 108.46 (C-2), 112.37 (C-4), 112.91 (C-6), 113.89 (C-10), 129.78 (C-5), 140.54 (C-8), 151.51(C-3), 159.64 (C-1), 169.39(C-11): m/z : 224 (100), 207 (34), 179 (40), 164 (22) : ν_{max} (cm^{-1}) 3150, 3010, 2900 (C-H), 1760 (C=O). λ_{max} (MeOH) 235nm (ε=10300), 272nm (ε=6437)

6.8 Preparation of 3-(2-methylallyloxy)-phenol (36)

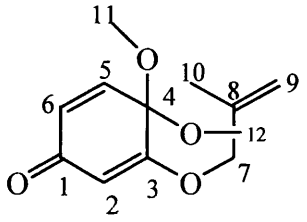


To a dry round bottomed flask (50ml) containing a magnetic follower was added 3-(2-methylallyloxy)-phenylacetate (**32b**) (0.501g, 2.43 x 10^{-3}mol) and 2M NaOH solution ($20cm^3$). The flask was fitted with a reflux condenser and the the reaction was allowed to reflux for 1 hour in an oil bath. The reaction was then allowed to cool in an ice bath before 2M H_2SO_4 was added whilst stirring until the pH of the solution had reached 2.The product was then extracted using chloroform (3x30ml) and these combined extracts were washed with saturated $NaCO_3$ solution to remove any acid salts still present. The chloroform layer was

dried over $MgSO_4$, filtered and evaporated to dryness. The residue was separated by flash column chromatography on neutral silica with CH_2Cl_2 to give **(36)** (0.324g, 1.97 x 10^{-3} mol, 81%) as a pale yellow oil.

Calc. mass of $C_{10}H_{12}O_2$ is 164.2040. δ_H ppm : 1.81 (1H, t, J=0.9Hz, H-9), 4.34 (2H, s, H-7), 4.98 (1H, q, J=0.9Hz, H-10), 5.08 (1H, q, J=0.9Hz, H-10), 5.41 (1H, s, OH), 6.42 (2H, m, H-2 and H-4 or H-6), 6.51 (1H, m, H-4 or H-6), 7.11 (1H, t, J=8.3Hz, H-5). δ_C ppm : 19.39 (C-9) , 71.76 (C-7), 102.38 (C-2), 107.26 (C-4 or C-6), 107.96 (C-4 or C-6), 112.89 (C-10), 130.09 (C-5), 140.78 (C-8), 156.66 (C-1), 160.08 (C-3). m/z : (CI) 182 (100), 165 (32), 123 (21). ν_{max} (cm^{-1}) 3365 (OH), 1603 (C=C). λ_{max} (MeOH) 231nm (ε=7158), 279nm (ε=6236)

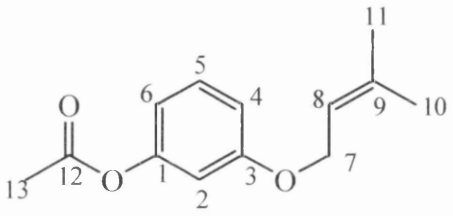
6.9 Preparation of 4,4-Dimethoxy-3-(2-methyl-allyloxy)-cyclohexa-2,5-dienone (41)



To a dry nitrogen flushed round bottomed flask (100ml), fitted with a septum and containing a magnetic follower was added (**36**), (0.512g, 3.121 x 10^{-3} mol) in dry methanol (15ml) and PIDA (2.006g, 6.22 x 10^{-3} mol) in dry methanol (15ml) with good stirring. The solution was stirred for 45 mins before addition of anhydrous K_2CO_3 (0.4g) to remove acetic acid. The reaction mixture was filtered, concentrated under vacuum and the product was immediately separated by flash column chromatography using CH_2Cl_2 as eluent, giving (**41**), (0.253g, 1.139 x 10^{-3} mol, 37% yield) as a yellow oil.

Observed mass was 222.2407. Calc. mass of $C_{12}H_{14}O_4$ is 222.2406. δ_H ppm : 1.83 ((3H, d, J=1.2Hz, H-10), 3.35 (6H, s, H-11 and H-12), 4.42 (2H, s, H-7), 5.04 (1H, d, J=1.2Hz, H-9), 5.10 (1H, s, H-9), 5.64 (1H, d, J=1.8Hz, H-2), 6.29 (1H, dd, J=1.8Hz, J=10.2Hz, H-6), 6.58 (1H, d, J=10.2Hz,H-5). δ_C ppm : 19.31 (C-10), 51.51 (C-11 and C-12), 72.62 (C-7), 94.09 (C-4), 105.02 (C-6), 114.59 (C-9), 131.08 (C-2), 138.50 (C-8), 140.81 (C-5), 168.32 (C-3), 186.39 (C-1). m/z (EI) : 225 (12), 193 (30), 169 (53), 141 (55), 128 (100), 55 (100). ν_{max} (cm^{-1}) :1680 (C=O), 1605 (C=C).

6.10 Preparation of 3-(3-methyl-but-2-enyloxy)-phenylacetate (32c)

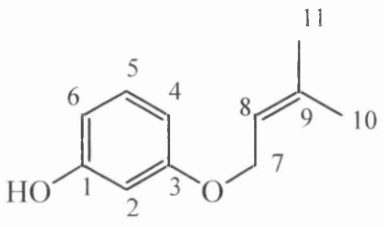


To a dry two necked round bottomed flask (100ml) containing a magnetic follower was added resorcinol monoacetate (5.001g, 33.0 x 10^{-3} mol), potassium carbonate (4.673g, 33.0 x 10^{-3} mol), KI (5.48g, 33.0 x 10^{-3} mol) and dry, distilled acetone (20cm^3). 4-bromo-2-methyl-but-2-ene (3.8ml, 33.0 x 10^{-3} mol) was added to the mixture via a syringe whilst stirring. The reaction was then allowed to reflux for 5 hours in an oil bath. Upon cooling, the reaction was washed with water (3x50ml). The combined aqueous layers were then extracted using diethyl ether (3x30ml) and all of the organic layers were washed with 2M NaOH solution. The organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography on neutral silica with CH_2Cl_2, to give

3-(3-methyl-but-2-enyloxy)-phenylacetate (**32c**), (5.758g, 26.16 x 10^{-3} mol, 58% yield) as a pale yellow oil.

Calc. mass of $C_{13}H_{16}O_3$ is 220.2520. δ_H ppm : 1.73 (3H, s, H-11), 1.79 3H, s, H-10), 2.28 (3H, s, H-13), 4.48 (2H, d, J=6.7Hz, H-7), 5.49 (1H, t, J=6.7Hz, H-8), 6.66 (2H, m, H-2 and H-4 or H-6), 6.78 (1H, m, H-4 or H-6), 6.82 (1H, t, J=8.0Hz, H-5). δ_C ppm: 18.172 (C-11), 21.127 (C-10), 25.80 (C-13), 64.49 (C-7), 108.25 (C-8), 112.37 (C-6), 113.66 (C-4), 119.32 (C-2), 129.73 (C-5), 138.43 (C-9), 151.56 (C-1), 159.77 (C-3), 169.37 (C-12). m/z (CI) 238 (21), 221 (16), 179 (8). ν_{max} (cm^{-1}): 3010, 2980, 2840 (C-H), 1762 (C=O). λ_{max} (MeOH) : 271nm (ε=11005)

6.11 Preparation of 3-(3-methyl-but-2-enyloxy)-phenol (37)

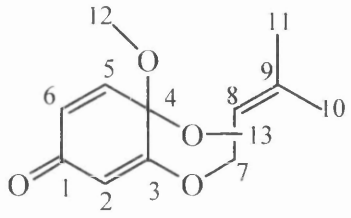


To a dry round bottomed flask (50ml) containing a magnetic follower was added 3-(3-methyl-but-2-enyloxy)-phenylacetate (0.511g, 2.32 x 10^{-3}mol) and 2M NaOH solution ($20cm^3$). The flask was fitted with a reflux condenser and the reaction was allowed to reflux for 1 hour in an oil bath. The reaction was then allowed to cool in an ice bath before 2M H_2SO_4 was added whilst stirring until the pH of the solution had reached 2.The product was then extracted using chloroform (3x30ml) and these combined extracts were washed with saturated $NaCO_3$ solution to remove any acid salts still present. The chloroform layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was separated by flash

column chromatography on neutral silica with CH_2Cl_2 to give (**37**), (0.243g , 1.36 x 10^{-3} mol, 59%) as a pale yellow oil.

Calc. mass of $C_{11}H_{14}O_2$ is 178.2309. δ_H ppm: 1.72 (3H, s, C-11), 1.77 (3H, s, C-10), 4.46 (2H, d, J=6.8Hz, H-7), 5.47(1H, t, J=6.8Hz, H-8), 5.63 (1H, s, O**H**), 6.42 (2H, m, H-2 and H-4 or H-6), 6.51 (1H, m, H-4 or H-6), 7.10 (1H, t, J=8.2Hz, H-5). δ_C ppm: 18.17 (C-10), 25.81 (C-11), 64.84 (C-7), 102.29 (C-2), 107.13 (C-4 or C-6), 107.85 (C-4 or C-6), 119.44 (C-8), 130.11 (C-5), 138.45 (C-9), 156.71 (C-3), 160.12 (C-1). m/z (CI) 196(10), 17 (100), 178 (9), 103 (24), 86 (35). ν_{max} (cm^{-1}) : 3425 (O-H), 2990 ,2890 ,2874 (C-H) λ_{max} (MeOH) : 228nm (ε= 5340), 282nm (ε=6730)

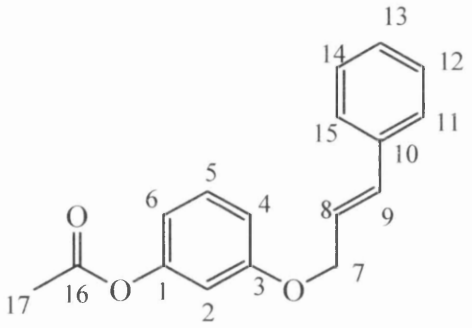
6.12 Preparation of 4,4-dimethoxy-3-(3-methylbut-2-enyloxy)-cyclohexa-2,5-dienone (44)



To a dry nitrogen flushed round bottomed flask (100ml), fitted with a septum and containing a magnetic follower was added **(37)**, (0.505g, 2.83 x 10^{-3} mol) in dry methanol (25ml) and PIDA (1.827g, 5.67 x 10^{-3} mol) in dry methanol (25ml) with good stirring. The solution was stirred for 45 mins before addition of anhydrous K_2CO_3 (1.5g) to remove acetic acid. The reaction mixture was filtered, concentrated under vacuum and the product was immediately separated by flash column chromatography using CH_2Cl_2 as eluent, giving **(44)**, (0.129g, 0.542 x 10^{-3} mol, 19% yield) as a yellow oil.

Observed mass was 238.2836. Calc. mass of $C_{13}H_{18}O_4$ is 238.2836. δ_H ppm : 1.73 (3H,d, J=0.7Hz, H-11), 1.78 (3H, d, J=0.9Hz, H-10), 3.32 (6H, s, H-12 and H-13), 4.51 (2H, d, J=6.8Hz, H-7), 5.44 (1H, t, J=6.8Hz, H-8), 5.64 (1H, d, J=1.9Hz, H-2), 6.32 (1H, dd, J=1.9Hz and J=10.2Hz, H-6), 6.57 (1H, d, J=10.2Hz, H-5). δ_C ppm : 18.25 (C-10), 25.75 (C-11), 51.47 (C-12 and C-13), 65.91 (C-7), 94.20 (C-2), 104.91 (C-4), 117.54 (C-8), 131.32 (C-6), 140.05 (C-9), 140.64 (C-5), 168.28 (C-3), 186.41 C-1).m/z (CI) : 239 (17), 207 (42), 188 (55), 171 (76), 124 (100). ν_{max} (cm^{-1}) : 1704 (C=O), 1623 (C=C), 1602 (C=C).

6.13 Preparation of 3-(3-phenyl-allyloxy)-phenylacetate (32d)

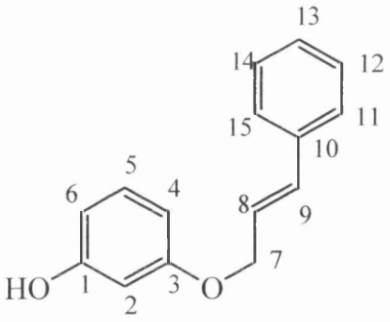


To a dry two necked round bottomed flask (100ml) containing a magnetic follower was added resorcinol monoacetate (5.028g, 33.0 x 10^{-3} mol), potassium carbonate (4.561g, 33 x 10^{-3} mol) and dry, distilled acetone (20cm^3). Cinnamyl bromide (4.012ml, 33 x 10^{-3} mol) was added to the mixture via a syringe whilst stirring. The reaction was then allowed to reflux for 5 hours in an oil bath. Upon cooling, the reaction was washed with water (3x50ml). The combined aqueous layers were then extracted using diethyl ether (3x30ml) and all of the organic layers were washed with 2M NaOH solution. The organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column

chromatography on neutral silica with CH_2Cl_2, to give 3-(3-phenyl-allyloxy)-phenylacetate (**32d**), (4.277g , 15.95 x 10^{-3} mol, 48% yield) as a pale yellow oil.

Calc. mass of $C_{17}H_{16}O_3$ is 268.3122 .δ_H ppm : 2.29 (3H, s, H-17), 4.68 (2H, q, J=4.3Hz and J=1.5Hz, H-7), 6.41 (1H, m, J=4.3Hz, H-8), 6.70 (3H, m, H-9, 2, 4 or 6), 6.82 (1H, m, H-4 or 6), 7.32 (6H, m, H-5, 11-15). δ_C ppm : 21.17 (C-17), 68.82 (C-7), 108.08 (C-2'), 108.49 (C-2), 112.38 (C-4), 114.01 (C-6), 124.2 (C-8), 126.6 (C-5), 127.96 (C-9), 128.60 -136.32 (C-11-15), 151.59 (C-1), 159.51 (C-3), 169.40 (C-16). m/z : (CI) 268 (100), 268 (15), 229 (12), 191 (29). ν_{max} (cm^{-1}) : 1765 (C=O), 1611 (C=C), 1600 (C=C). λ_{max} : 205nm (ε=2680), 252nm (ε=17210)

6.14 Preparation of 3-(3-phenyl-allyloxy)-phenol (38)

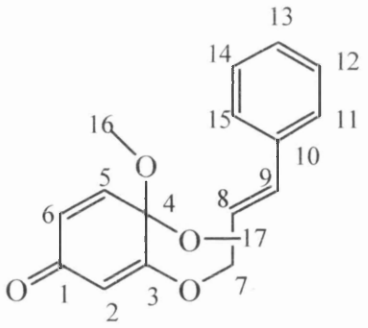


To a dry round bottomed flask (50ml) containing a magnetic follower was added 3-(3-phenyl-allyloxy)-phenylacetate (0.500g, 1.87 x 10^{-3}mol) and 2M NaOH solution ($20cm^3$). The flask was fitted with a reflux condenser and the the reaction was allowed to reflux for 1 hour in an oil bath. The reaction was then allowed to cool in an ice bath before 2M H_2SO_4 was added whilst stirring until the pH of the solution had reached 2.The product was then extracted using chloroform (3x30ml) and these combined extracts were washed with saturated $NaCO_3$ solution to remove any acid salts still present. The chloroform layer was

dried over $MgSO_4$, filtered and evaporated to dryness. The residue was separated by flash column chromatography on neutral silica with CH_2Cl_2 to give (**38**), (0.210g , 9.29 x 10^{-4} mol, 49%), as a pale yellow oil.

Calc. mass of $C_{15}H_{14}O_2$ is 226.2749. δ_H ppm : 4.62 (2H, s, H-7), 6.30 – 6.91 (6H, m, complex, H-8,9,2 and 4-6), 7.14-7.36 (5H, m, H-11-15). δ_C ppm : 75.1 (C-7), 102.1 (C-2), 106.4 (C-4 or 6), 107.9 (C-4 or 6), 125.2 (C-8), 126.4 (C-11 and 15), 127.2 (C-9), 128.7 (C-12 and 14), 129.5 (C-13), 132.1 (C-5), 156.1 (C-1), 160.6 (C-3). m/z : (CI) 244 (8), 227 (20), 134 (100), 117 (100), 58 (82). ν_{max} (cm^{-1}) : 3350 (C=O), 1620 (C=C), 1590 (C=C). λ_{max} (MeOH) : 292.1nm (ε=1302), 282.1nm (ε=4601), 251.7nm (ε=22259), 209.5nm (ε=2680)

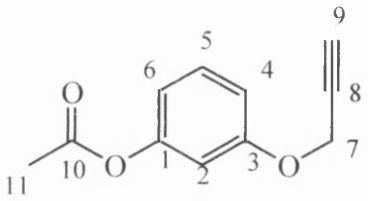
6.15 Preparation of 4,4-Dimethoxy-3-(3-phenyl-allyloxy)-cyclohexa-2,5-dienone (47)



To a dry nitrogen flushed round bottomed flask (100ml), fitted with a septum and containing a magnetic follower was added **(38),** (0.500g, 2.212 x 10^{-3} mol) in dry methanol (15ml) and PIDA (1.424g, 4.424 x 10^{-3} mol) in dry methanol (15ml) with good stirring. The solution was stirred for 45 mins before addition of anhydrous K_2CO_3 (1.2g) to remove acetic acid. The reaction mixture was filtered, concentrated under vacuum and the product was immediately separated by flash column chromatography using CH_2Cl_2 as eluent, giving **(47),** (3.035g , 1.06 x 10^{-2} mol, 48% yield) , as a yellow oil.

Observed mass was 286.3274. Calc. mass for $C_{17}H_{18}O_4$ is 286.3275. δ_H ppm : 3.35 (6H, s, H-16 and 17), 4.67 (2H, d, J=6.2Hz, H-7), 5.71 (1H, d, J=1.7Hz, H-2), 6.34 (2H, m, H-8 and H-5 or H-6), 6.61 (1H, d, J=10.2Hz, H-5 or H-6), 6.73 (1H, d, J=15.9Hz, H-9), 7.35 (5H, m, H-11-15). δc ppm : 51.54 (C-16 and C-17), 69.69 (C-7), 94.18 (C-4), 105.08 (C-8), 121.64 (C-9), 126.72 (C-11 and C-15), 128.40 (C-6), 128.66 (C-12 and C-14), 131.22 (C-5), 135.22 (C-10), 135.69 (C-13), 140.66 (C-2), 168.05 (C-3), 186.29 (C-1). m/z : (CI) 304 (5), 287 (12), 255 (10), 117 (100). $\nu_{max}(cm^{-1})$: 1720 (C=O), 1610 (C=C), 1580 (C=C). λ_{max} (MeOH) : 232.2 nm (ε=4250), 265.5nm (ε=1820)

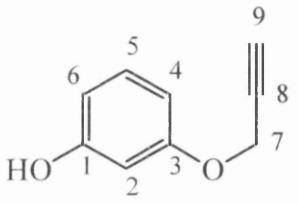
6.16 Preparation of 3-prop-2-ynyloxy-phenylacetate (48)



To a dry two necked round bottomed flask (100ml) containing a magnetic follower was added resorcinol monoacetate (1.503g, 9.88 x 10^{-3} mol), potassium carbonate (1.366g, 9.88 x 10 -3mol) and dry, distilled acetone (20cm^3). Propargyl bromide (1.176g, 9.88 x 10 $^{-3}$mol) was added to the mixture via a syringe whilst stirring. The reaction was then allowed to reflux for 5 hours in an oil bath. Upon cooling, the reaction was washed with water (3x50ml). The combined aqueous layers were then extracted using diethyl ether (3x30ml) and all of the organic layers were washed with 2M NaOH solution. The organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography on neutral silica with CH_2Cl_2, to give 3-prop-2-ynyloxy-phenylacetate (**48**), (1.102g, 5.80 x 10^{-3} mol, 59 % yield), as a pale yellow oil.

Observed mass was 190.1986. Calc. mass for $C_{11}H_{10}O_3$ is 190.1986. δ_H ppm: 2.25 (3H, s, H-11), 2.53 (1H, t, J=2.4Hz, H-9), 4.67 (2H, d, J=2.4Hz, H-7), 6.72 (2H, m, H-2 and H-4 or H-6), 6.86 (1H, m, H-4 or H-6), 7.29 (1H,t, J=8.4Hz, H-5). δc ppm : 21.15 (C-11), 55.96 (C-7), 75.82 (C-9), 78.16 (C-8), 108.72 (C-2), 112.40 (C-4 or C-6), 114.72 (C-4 or C-6),129.86 (C-5), 151.51 (C-3), 158.35 (C-1), 169.32 (**C**O). m/z (CI) 208 (100), 191 (12), 147 (21).ν_{max} (cm^{-1}) 3292 (C≡C), 3075, 3032, 2928 (C-H), 1760 (C=O). λ_{max} : 265.6nm (ε=13661), 259.1nm (ε=14231), 234.4nm (ε=3453)

6.17 Preparation of 3-prop-2-ynyloxy-phenol (49)

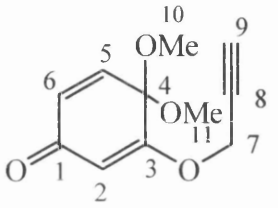


To a dry round bottomed flask (50ml) containing a magnetic follower was added **(48),** (1.000g, 5.291 x 10^{-3}mol) and 2M NaOH solution (100cm^3). The flask was fitted with a reflux condenser and the reaction was allowed to reflux for 1 hour in an oil bath. The reaction was then allowed to cool in an ice bath before 2M H_2SO_4 was added whilst stirring until the pH of the solution had reached 2.The product was then extracted using chloroform (3x30ml) and these combined extracts were washed with saturated $NaCO_3$ solution to remove any acid salts still present. The chloroform layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was separated by flash column chromatography on neutral silica with CH_2Cl_2 to give **(49),** (0.66g , 4.45 x 10^{-3} mol, 84% yield).

Calc. mass of $C_9H_8O_2$ is 148.1613. δ_H ppm : 2.52 (1H,t, J=2.4Hz, H-9), 4.64 (2H, d, J=2.4Hz ,H-7), 5.67 (1H, s (broad), O**H**), 6.47 (2H, m, H-2 and H-4 or H-6), 6.49 (1H, m, H-

4 or H-6), 7.13 (1H, t, J=8.4Hz, H-5). δ_C ppm : 55.87 (C-7), 75.69 (C-9), 78.45 (C-8), 102.64 (C-2), 107.16 (C-4 or C-6), 108.84 (C-4 or C-6), 130.22 (C-5), 156.71 (C-3), 158.79 (C-1). m/z (EI) 148 (40), 147 (100), 131 (12) .ν_{max} (cm^{-1}) 3460 (O-H), 3290 (C≡C), 2961, 2927, (C-H), 1600 (C=C aromatic). λ_{max} : 264nm (ε=1737)

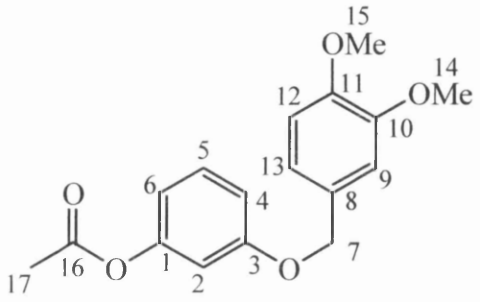
6.18 Preparation of 4,4-Dimethoxy-3-prop-2-ynyloxy-cylohexa-2,5-dienone (42)



To a dry nitrogen flushed round bottomed flask (100ml), fitted with a septum and containing a magnetic follower was added **(49),** (0.500g, 3.37 x 10^{-3} mol) in dry methanol (15ml) and PIDA (2.171g, 6.76 x 10^{-3} mol) in dry methanol (15ml) with good stirring. The solution was stirred for 45 mins before addition of anhydrous K_2CO_3 (1.2g) to remove acetic acid. The reaction mixture was filtered, concentrated under vacuum and the product was immediately separated by flash column chromatography using CH_2Cl_2 as eluent, giving **(52),** (0.341g , 1.63 x 10^{-3} mol, 48% yield) , as a yellow oil.

Observed mass was 208.0737. Calc. mass for $C_{11}H_{18}O_4$ is 208.0736. δ_H ppm : 2.43 (1H, s, H-9), 3.24 (6H, s, H-10 and H-11), 4.69 (2H, s, H-7), 5.71 (1H, d, J=1.9Hz, H-2), 6.32 (1H, d, J=8.6Hz, H-5), 6.55 (1H, dd, J=1.9Hz and J=8.5Hz, H-6). δ_C ppm : 51.11 (C-10 and C-11), 68.21 (C-7), 77.2 (C-9), 86.99 (C-8), 96.8 (C-2), 98.86 (C-4), 131.11 (C-6), 146.21 (C-5), 176.98 (C-3), 186.55 (C-1). m/z (EI) : 208 (21), 193 (35), 189 (87), 170 (53) 131 (76). ν_{max} (cm^{-1}) : 3307, 3019, 2940 (C-H), 1669 (C=O). λ_{max} : 242.7nm (ε=1542), 284.5nm (ε=766)

6.19 Preparation of 3-(3,4-dimethoxy -benzyloxy)-phenylacetate (58)

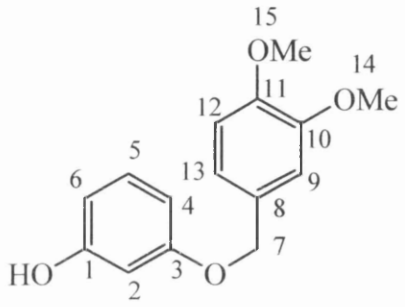


To a dry two necked round bottomed flask (100ml) containing a magnetic follower was added resorcinol monoacetate (5.180g, 34.00 x 10^{-3} mol), potassium carbonate (4.581g, 35.00 x 10^{-3} mol) and dry, distilled acetone (20cm^3). Freshly prepared veratryl bromide (7.672g, 33.20 x 10^{-3} mol) was added to the mixture via a syringe whilst stirring. The reaction was then allowed to reflux for 5 hours in an oil bath. Upon cooling, the reaction was washed with water (3x50ml). The combined aqueous layers were then extracted using diethyl ether (3x30ml) and all of the organic layers were washed with 2M NaOH solution. The organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography on neutral silica with CH_2Cl_2, to give 3-(3,4-dimethoxy-benzyloxy)-phenylacetate **(58),** (7.489g, 24.79 x 10^{-3} mol, 79 % yield), as a pale yellow oil.

Calc. mass of $C_{17}H_{18}O_5$ is 302.3269. δ_H ppm: 2.29 (3H, s, H-17), 3.90 (3H, s, H-15), 3.89 (3H, s, H-14), 4.96 (2H, s, H-7), 6.73 - 6.95 (6H, m, H-2,4,6,9,12 and 13), 7.28 (1H, t, J=8.1Hz, H-5'). δc ppm : 21.14 (C-17),55.87 (C-15), 55.92 (C-14), 70.27 (C-7), 108.57 (C-2), 111.00 (C-12), 111.02 (C-9),112.43 (C-4), 114.03 (C-6), 120.34 (C-13), 128.97 (C-8),

129.84 (C-5), 148.96 (C-15), 149.12 (C-14), 151.56 (C-3), 159.66 (C-1), 169.40 (C-16). m/z (EI) : 302 (21), 271 (43), 240 (56), 149 (100). ν_{max} (cm^{-1}) : 1767 (C=O), 1620 (C=C), 1587 (C=C). λ_{max} (CH_2Cl_2) : 272.4nm (ε=19328)

6.20 Preparation of 3-(3,4-dimethoxy-benzyloxy) -phenol (53)

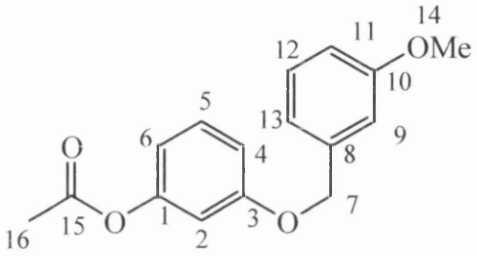


To a dry round bottomed flask (50ml) containing a magnetic follower was added **(58),** (6.008g, 19.01 x 10^{-3} mol) and 2M NaOH solution ($300cm^3$). The flask was fitted with a reflux condenser and the reaction was allowed to reflux for 1 hour in an oil bath. The reaction was then allowed to cool in an ice bath before 2M H_2SO_4 was added whilst stirring until the pH of the solution had reached 2.The product was then extracted using chloroform (3x50ml) and these combined extracts were washed with saturated $NaCO_3$ solution to remove any acid salts still present. The chloroform layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was separated by flash column chromatography on neutral silica with CH_2Cl_2 to give **(53),** (4.127g , 15.87 x 10^{-3} mol, 80% yield) as a thick yellow oil.

Observed mass was 260.2896. Calc. mass for $C_{15}H_{16}O_4$ is 260.2896. δ_H ppm : 3.88 (3H, s, H-15), 3.89 (3H, s, H-14), 4.94 (2H, s, H-7), 5.54 (1H, s (broad),O**H**), 6.43 – 6.95 (6H, m, H-2,4,6,9,12 and 13) 7.14 (1H, t, J=8.0Hz, H-5). δc ppm : 55.87 (C-14), 55.93 (C-

15), 70.08 (C-7), 102.44 (C-2), 107. 221 (C-9 or C-12), 108.07 (C-9 or C-12), 111.01 (C-6), 111.08 (C-4), 120.34 (C-13), 129.33 (C-8), 130.13 (C-5), 148.84 (C-10), 149.06 (C-11), 156.83 (C-3), 160.13 (C-1). m/z (EI) : 260 (18) , 243 (45), 151 (80), 109 (78). ν_{max} (cm^{-1}) : 3421 (C-OH), 1610 (C=C), 1580 (C=C). λ_{max} : (CH_2Cl_2) 276.7nm (ε=13650)

6.21 Preparation of 3-(3-methoxy -benzyloxy)-phenylacetate (61)

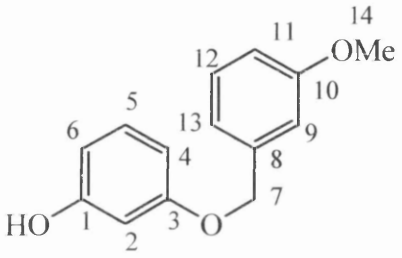


To a dry two necked round bottomed flask (100ml) containing a magnetic follower was added resorcinol monoacetate (4.101g, 31.60 x 10^{-3} mol), potassium carbonate (4.372g, 31.60 x 10^{-3} mol) and dry, distilled acetone ($30cm^3$). Freshly prepared 3-methoxybenzyl bromide (6.410g, 31.90 x 10^{-3} mol) was added to the mixture via a syringe whilst stirring. The reaction was then allowed to reflux for 5 hours in an oil bath. Upon cooling, the reaction was washed with water (3x50ml). The combined aqueous layers were then extracted using diethyl ether (3x30ml) and all of the organic layers were washed with 2M NaOH solution. The organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography on neutral silica with CH_2Cl_2, to give 3-(3-methoxy-benzyloxy)-phenylacetate **(61)**, (5.721g, 21.03 x 10^{-3} mol, 80 % yield), as a pale yellow oil.

Calc. mass of $C_{16}H_{16}O_4$ is 272.3006.δ_H ppm: 2.31 (3H, s, H-16), 3.84 (3H, s, H-14), 5.04 (2H, s, H-7), 6.76 (2H, m, Ph), 6.90 - 7.33 (8H, m, complex, H-2, 4-6 and H-9,11-13).

δc ppm : 21.14 (C-16), 55.23 (C-14), 70.06 (C-7), 108.64 (C-2), 112.43 (C-12), 112.92 (C-13),113.65 (C-4), 114.19 (C-6), 119.69 (C-9), 129.70 (C-11), 129.91 (C-5), 138.23 (C-8), 151.65 (C-3), 159.87 (C-10), 160.02 (C-1), 169.39 (C-15). m/z (EI) : 272 (61), 241 (13), 210 (32), 137 (100). ν_{max} (cm^{-1}) : 1762 (C=O), 1610 (C=C), 1599 (C=C). λ_{max} (CH_2Cl_2) : 269.2 nm (ε=19040)

6.22 Preparation of 3-(3-methoxy-benzyloxy) -phenol (62)

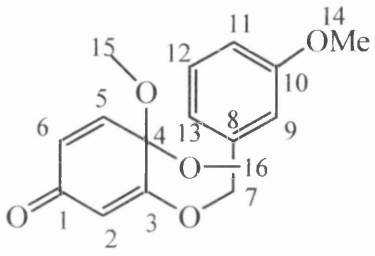


To a dry round bottomed flask (50ml) containing a magnetic follower was added **(62)**, (5.723g, 21.04 x 10^{-3}mol), 2M NaOH solution ($200cm^3$) and a minimal amount of THF to dissolve the ester. The flask was fitted with a reflux condenser and the reaction was allowed to reflux for 1 hour in an oil bath. The reaction was then allowed to cool in an ice bath before 2M H_2SO_4 was added whilst stirring until the pH of the solution had reached 2.The product was then extracted using chloroform (3x50ml) and these combined extracts were washed with saturated $NaCO_3$ solution to remove any acid salts still present. The chloroform layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was separated by flash column chromatography on neutral silica with CH_2Cl_2 to give **(62)**, (3.941g, 17.13 x 10^{-3} mol, 81.5 % yield) as a thick yellow oil.

Calc. mass of $C_{14}H_{14}O_3$ is 230.2633.δ_H ppm : 3.78 (3H, s, H-14), 4.95 (2H, s, H-7), 5.57 (1H, s (broad),**OH**), 6.43 (2H, m, Ph), 6.54 - 7.26 (8H, m, complex, H-2,4-6 and H-9,11-

13). δc ppm : 55.27 (C-14), 69.86 (C-7), 102.46 (C-2), 107. 34 (C-9), 108.17 (C-11), 112.92 (C-6), 113.56 (C-4), 119.77 (C-13), 129.66 (C-12), 130.19 (C-8), 138.44 (C-5), 156.68 (C-10), 159.66 (C-3), 159.98 (C-1). m/z (EI): 230 (M+, 76), 213 (23), 121 (54). ν_{max} (cm^{-1}) : 3404 (C-OH), 1600 (C=C),1595 (C=C). λ_{max} : (CH_2Cl_2) 269.6nm (ε=11979).

6.23 Preparation of 4,4-dimethoxy-3-(3-methoxybenzyloxy)-cyclohexa-2,5-dienone (63)

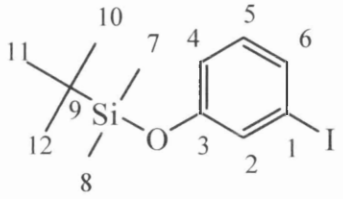


To a dry nitrogen flushed round bottomed flask (100ml), fitted with a septum and containing a magnetic follower was added **(62),** (0.758g, 3.30 x 10^{-3}mol) in dry methanol (30ml) and PIDA, (2.124g, 6.60 x 10^{-3}mol) in dry methanol (45ml) with good stirring. The solution was stirred for 45 mins before addition of anhydrous K_2CO_3 (2.0g) to remove acetic acid. The reaction mixture was filtered, concentrated under vacuum and the product was immediately separated by flash column chromatography using CH_2Cl_2 as eluent, giving. **(63),** (0.154g, 0.531 x 10^{-3} mol, 16% yield) as a yellow oil.

Calc. mass for $C_{16}H_{18}O_5$ is 290.3659 .δ_H ppm : 3.34 (6H, s, H-15 and H-16), 3.80 (3H, s, H-14), 5.03 (2H, s, H-7), 5.69 (1H, d, J=1.9Hz, H-2), 6.30 (1H, dd, J= 1.9Hz, 10.4Hz, H-6), 6.59 (1H, d, J= 10.4Hz, H-5), 6.88 (1H, m, H-13), 6.96 (2H, m, H-9 and H-11) 7.28 (1H,q, J=8.0Hz, H-12). δc : 51.56 (OCH_3), 55.22 (OCH_3), 70.61 (C-1), 94.17 (**C**-OMe), 105.49 (C-2'), 113.04 (C-5'), 114.03 (C-6'), 119.70 (Ph), 129.86 (Ph), 131.16 (Ph), 136.17

(Ph), 140.79 (Ph), 159.00 (C-4'), 168.09 (C-3'), 186.25 (C-1'). m/z (EI): 290 (32), 169 (85), 121 (51), 91 (86) . ν_{max} (cm^{-1}) : 1667 (C=O), 1631 (C=C), 1602 (C=C). λ_{max} : (CH_2Cl_2) 284.1nm (ε=1370), 243.2nm (ε=13775)

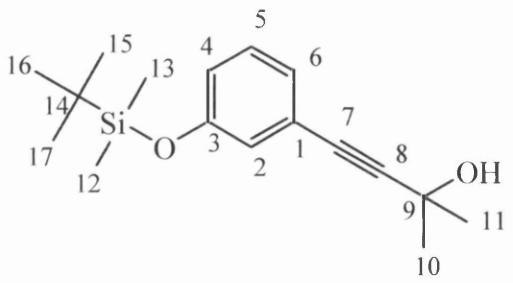
6.24 Preparation of 3-tert-butyldimethylsiloxy-1-iodobenzene (82)



To a round bottomed flask (100ml) containing a magnetic follower was added 3-iodophenol (10.10g, 0.045mol), *tert*-butyldimethylsilyl chloride (7.007g, 0.046mol), and imidazole (6.452g, 0.095mol) in dichloromethane (60ml). The mixture was then stirred for 18hours, during which a white solid precipitated, and was removed by filtration. The filtrate was concentrated under vacuum, and the residue purified by flash column chromatography on silica using dichloromethane. The product **(82)** (15.11g, 0.045mol, 99.8 %) was obtained as a colourless oil. (lit.ref. [60] n.m.r.)

Observed mass was 334.0250. Calc. for $C_{12}H_{19}OSiI$ is 334.0252. δ_H, 0.19 (6H, s, H-7,8), 0.97 (9H, s, H-10,11,12), 6.85 (1H, dd, J=1.6Hz, 8.0Hz, H-4), 6.94 (1H, t, J=8.0Hz, H-5), 7.22 (1H, d, J-1.6Hz H-2), 7.28 (1H, dd, J=1.6Hz, 8.0, H-6). δ_C, ppm, -4.49 (C-7,8), 18.14 (C-9), 25.58 (C-10,11,12), 94.09 (C-1), 119.45 (C-4), 129.39 (C-2), 130.43 (C-6), 130.64 (C-5), 156.25 (C-3). m/z (EI), 334(35), 227(80), 150(100), 135(58), 115(28), 91(24), 75(18), 73(56), 57(33). ν_{max} (cm^{-1}), 2956, 2930, 2886, 2858 (C-H), 1584, 1471. λ_{max} (MeOH), 210.9nm (ε=36185), 228.2nm (ε= 16254), 273.8nm (ε= 4784).

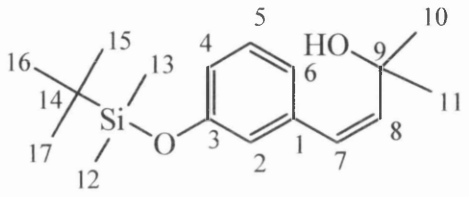
6.25 Preparation of 4-(3'-tert-butyldimethylsiloxyphenyl)-2-methylbut-3-yn-ol (83)



To a round bottomed flask (100ml) containing a magnetic follower was added **(82)** (1.01g, 2.99×10^{-3} mol), 2-methyl-3-butyn-2-ol (0.63g, 7.2×10^{-3}mol), $Pd(PPh_3)_2Cl_2$ (0.057g, 8.1×10^{-5} mol) and CuI (0.015g, 8.1×10^{-5} mol) in diisopropylamine (50ml). A water condenser was then attached to the top of the flask, and the stirred solution was then raised to 75°C using an oil bath. This temperature was maintained for 16 hours before the solution was allowed to cool to room temperature. A white solid (10.57g) had been formed, and this was removed by filtration. The filtrate was then concentrated under vacuum to yield a black tar which was purified by flash column chromatography using gradient elution with 30/40 pet spirit and dichloromethane. Elution with pure dichloromethane afforded **(83)** (1.16g, 2.99×10^{-3} mol, 100%) as a dark brown oil. (lit.ref.[60] n.m.r.)

Observed mass was 290.1702. Calc. for $C_{17}H_{26}O_2Si$ is 290.1702. δ_H, 0.20 (6H, s, H-12,13), 0.99 (9H, s, H-15,16,17), 1.62 (6H, s, H-10,11), 6.79 (1H, d, J=7.8Hz, 1.4Hz, H-4), 6.90 (1H, s, H-2), 7.02 (1H, d, J=7.8Hz, 1.4Hz, H-6), 7.15 (1H, t, J=7.8Hz, H-5). δ_C, ppm, -4.44 (C-12,13), 18.15 (C-14), 25.63 (C-15,16,17), 31.46 (C-10,11), 65.59 (C-9), 81.96 (C-8), 93.50 (C-7), 120.52 (C-4), 123.16 (C-2), 123.72 (C-1), 124.88 (C-6), 129.29 (C-5), 155.39 (C-3). m/z (EI), 290(48), 273(11), 233(100), 215(29), 159(17), 115(13), 75(57), 73(15), 57(12). ν_{max} (cm^{-1}), 3348 (O-H), 2981, 2956, 2930,2896, 2859 (C-H), 1596, 1576, 1480. λ_{max} (MeOH), 210.6nm (ε= 23973), 240.4nm (ε= 10682), 250.4nm (ε= 12663), 285.6nm (ε= 1402).

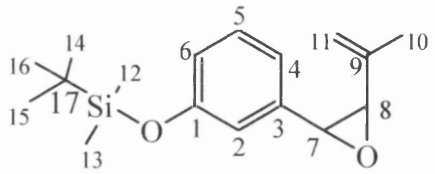
6.26 Preparation of Z-4-(3'-tert-butyldimethylsiloxyphenyl)-2-methylbut-3-en-2-ol (76a)



To a round bottomed flask (100ml) containing a magnetic follower was added **(83)** (2.015g, 6.95×10^{-3} mol), Lindlar catalyst (0.198g) and methanol (25ml). The flask was then placed on a hydrogenator at atmospheric pressure, and the apparatus evacuated, purged with hydrogen, evacuated again, and repurged with hydrogen. The reaction was monitored until one equivalent of hydrogen had been consumed. The Lindlar catalyst was filtered off, and the filtrate concentrated under vacuum. The products were separated by flash column chromatography using gradient elution with 40/60 pet spirit and dichloromethane. Elution with pure dichloromethane afforded **(76a)** (1.79g, 6.26×10^{-3} mol, 89 %) as a yellow oil. Lit. ref.[60] n.m.r.)

Observed mass was 292.1859. Calc. mass for $C_{17}H_{28}O_2Si$ is 292.1858. δ_H, 0.19 (6H, s, H-12,13), 0.98 (9H, s, H-15,16,17), 1.34 (6H, s, H-10,11), 1.78 (1H, s, O*H*), 5.73 (1H, d, J=12.6, H-8), 6.40 (1H, d, J=12.6, H-7), 6.72 (1H, d, J=7.8Hz, H-4), 6.85 (1H, s, H-2), 6.90 (1H, d, J=7.8Hz, H-6), 7.16 (1H, t, J=7.8Hz, H-5). δ_C, ppm, -4.41 (C-12,13), 18.17 (C-14), 25.66 (C-15,16,17), 31.11 (C-10,11), 71.98 (C-9), 118.81 (C-8), 120.57 (C-7), 121.98 (C-2), 127.59 (C-6), 129.12 (C-4), 138.91 (C-1), 139.33 (C-5), 155.88 (C-3). m/z (EI), 292(23), 277(15), 235(35), 217(75), 115(8), 75(100). m/z (CI), 175(100), 91(5). ν_{max} (cm^{-1}), 3417 (O-H), 2958, 2859 (C-H). λ_{max} (MeOH), 208.7nm (ε= 18360), 246.0nm (ε= 5512).

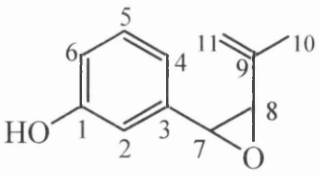
6.27 Preparation of (tert-Butyl- [3-(3-isoprenyl-oxiranyl)]-phenoxyl-dimethylsilane (89)



To a stirred solution of protected alcohol **(88a),** (0.051g, 16.22 x 10^{-3} mol) in dry pet. spirit 40/60 (0.7ml), and dry pyridine (0.5ml) at 0°C, was added dropwise to a solution of thionyl chloride (16µl, 16.22 x 10^{-3} mol), in pet. spirit 40/60 (0.4ml). The reaction was allowed to proceed at 0°C and was followed by tlc. Once the starting material had disappeared the reaction mixture was concentrated under vacuum and the product was immediately purified by flash chromatography using CH_2Cl_2 as eluent giving **(89),** (0,039g, 0.134 x 10^{-3} mol, 83% yield) as a pale yellow oil.

Calc. mass of $C_{17}H_{26}SiO_2$ is 290.4774. δ_H ppm : 0.17 (6H, s, H-12 and 13), 0.97 (9H, s, H-14,15 and 16), 1.49 (3H, d, J= 2.1Hz, H-10), 3.65 (1H, m, H-8), 4.14 (1H, d, J=4.4Hz, H-7), 4.88 (1H, s, H-11), 4.99 (1H, q, H-11), 6.74 (2H, m, H-2 and H-6 or H-4), 6.88 (1H, m, H-4 or H-6), 7.14 (1H, m, H-5). δ_C ppm : -4.42 (C-12 and 13), 18.19 (C-17), 19.23 (C-10), 25.66 (C-14,15 and 16), 58.27 (C-8), 61.02 (C-9), 113.45 (C-2), 119.34 (C-11), 119.79 (C-4 and C-6), 128.69 (C-5), 136.27 (C-9), 137.24 (C-3), 155.20 (C-1). m/z (EI) 290 (19), 275 (28), 261 (35), 233 (67), 203 (87). ν_{max} (cm^{-1}) : 1600, 1590 (C=C). λ_{max} (CH_2Cl_2) : 242.4nm (ε=11022), 269.8 nm (ε=1288)

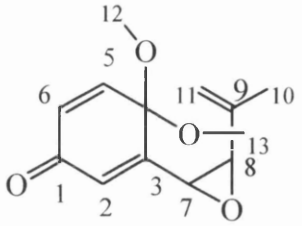
6.28 Preparation of 3-(3-isoprenyl –oxiranyl) phenol (85)



To a dry round bottomed flask (100ml) containing a magnetic follower was added **(89)**, (0.110g, 0.37 x 10^{-3} mol) and CsF (0.058g, 0.37 x 10^{-3} mol) in methanol (50ml). The reaction was stirred for 10hrs, concentrated under vacuum, dissolved in CH_2Cl_2 (50ml), washed with water (2 x 50ml), dried over $MgSO_4$ and concentrated under vacuum. The product was purified by flash column chromatography to yield **(85)**, (0.063g, 0.358 x 10^{-3} mol, 95% yield).

Calc. mass of $C_{11}H_{12}O_2$ is 176.2150. δ_H ppm: 1.49 (3H, d, J=1.9Hz, H-10), 3.69 (1H, m, H-8), 4.19 (1H, d, J=4.6Hz, H-7), 4.88 (1H, s, H-11), 4.97 (1H,m, H-11) 6.12 (1H, s (broad), O**H**), 6.79 (3H, m, H-2, H-4 and H-6), 7.15 (1H, t, J-7.6Hz, H-5). δ_C ppm : 19.20 (C-10), 58.64 (C-8), 61.43 (C-7), 113.65 (C-11), 114.74 (C-4 and C-6), 119.02 (C-2), 129.90 (C-5), 135.88 (C-9), 136.91 (C-3), 155.26 (C-1). m/z (EI) : 177 (68), 158 (100), 147 (90), 133 (30). ν_{max} (cm^{-1}) : 3392 (C=O), 3094 (C-H), 1601 (C=C).

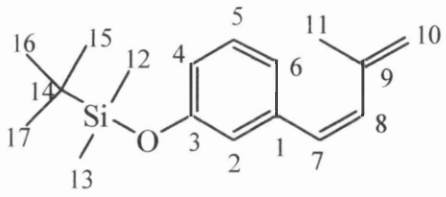
6.29 Preparation of 3-(3-isopropenyl-oxiranyl)-4,4-dimethoxy-cyclohexa-2,5-dienone (90)



To a dry nitrogen flushed round bottomed flask (100ml), fitted with a septum and containing a magnetic follower was added **(85)**, (0.123g, 0.69 x 10^{-3}mol in dry methanol (15ml) and PIDA, (0.451g, 1.40 x 10^{-3}mol) in dry methanol (15ml) with good stirring. The solution was stirred for 45 mins before addition of K_2CO_3 (0.4g) to remove acetic acid. The reaction mixture was filtered, concentrated under vacuum and the product was immediately separated by flash column chromatography using CH_2Cl_2 as eluent giving **(90)**, (0.068g, 0.29 x 10^{-3}mol, 41% yield) as a yellow oil.

Calc. mass of $C_{13}H_{16}O_4$ is 236.2767. δ_H ppm : 1.71 (3H, s, H-11), 3.29 (3H, s, H-13), 3.35 (3H, s, H-12), 3.75 (1H, d, J=4.7Hz, H-8), 3.97 (1H, dd, J=4.7Hz and J=0.9Hz, H-7), 4.90 (1H, s, H-10), 4.98 (1H, s, H-10), 6.14 (1H, dd, J=2.1Hz and J=0.9Hz, H-2), 6.36 (1H, dd, J=10.4Hz and J=2.1Hz,H-6), 6.85 (1H, d, J=10.4Hz, H-5). δ_C ppm: 19.30 (C-11), 50.76 (C-13), 51.37 (C-12), 55.38 (C-8), 62.23 (C-7), 94.77 (C-4), 113.58 (C-10), 127.74 (C-6), 131.82 (C-2), 135.98 (C-9), 142.13 (C-5), 150.26 (C-3), 184.47 (C-1). m/z (EI) : 236 (15), 205 (60), 177 (32), 85 (100). ν_{max} (cm^{-1}) : 2945 (C-H), 1677 (C=O), 1622 (C=C). λ_{max} : 267.4 nm (ε=7634), 246.9 nm (ε=3351).

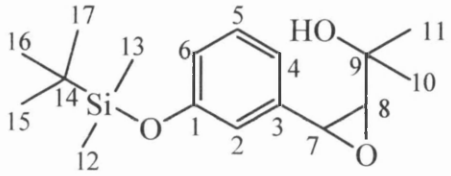
6.30 tert-Butyl-dimethyl-[3-(3-methyl-buta-1,3-dienyl)-phenoxy]-silane (77)



To a stirred solution of protected alcohol **(76a),** (0.251g, 0.859 x 10^{-3} mol) in dry pet. spirit 40/60 (0.7ml), and dry pyridine (1.0ml) at 0°C, was added dropwise to a solution of thionyl chloride (0.1ml, 0.859 x 10^{-3} mol), in pet. spirit 40/60 (1.0ml). The reaction was allowed to proceed at 0°C and was followed by tlc. Once the starting material had disappeared the reaction mixture was concentrated under vacuum and the product was immediately purified by flash chromatography using CH_2Cl_2 as eluent giving **(77),** (0.146g, 0.532 x 10^{-3} mol, 62 % yield) as a pale yellow oil.

Calc. mass for $C_{17}H_{26}OSi$ is 274.1753. δ_H ppm: 0.19 (6H, s, H-12 and H-13), 0.98 (9H, s, H-15,16 and 17), 4.99 (2H, d, J=1.6Hz, H-10), 6.38 (1H, dd, J= 1.6Hz and J=17.3Hz, H-8), 6.58 (1H, d, J=17.2Hz, H-7), 6.74 (2H, m, H-2 and H-4 or 6), 6.82 (1H, m, H-4 or 6), 7.11 (1H, t, J=8.1Hz, H-5) δ_C ppm: -4.22 (C-12 and 13), 18.9 (C- 14), 23.44 (C-15,16 and 17), 25.67 (C-11), 104.71 (C-10), 121.11 (C-2), 123.29 (C-4 or 6), 123.87 (C-4 or 6), 129.96 (C-8), 131.46 (C-7), 132.10 (C-5), 137.87 (C-1), 147.12 (C-9), 160.13 (C-3). m/z (EI) : 275 (11), 261 (19), 260 (23), 230 (59), 201 (87). ν_{max}: 3221, 3019, 3002 (C-H).

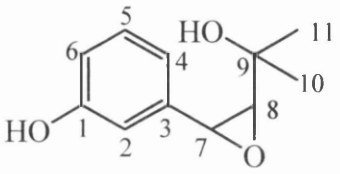
6.31 cis-4-(3'- tert-butyldimethylsilyloxyphenyl)-2 methyl-3,4-oxiranylbutan-2-ol (88a)



A dry round bottomed flask (50ml) was charged with a magnetic follower, fitted with a septum and flushed three times with nitrogen.**(76a)** (0.245g, 8.548 x 10^{-3} mol) in dry CH_2Cl_2 (10ml) was added by syringe and kept at 0°C, and to this solution was added a solution of *m*-chloroperbenzoic acid (1.475g,8.548 x 10^{-3} mol) in dry CH_2Cl_2(3ml) at 0°C *via* a double ended needle. The reaction mixture was stirred under nitrogen at 0°C for 2 hours. The precipitated *m*-chlorobenzoic acid was removed by filtration, the precipitate washed with CH_2Cl_2 (2 x 10ml) and the combined filtrates dried ($MgSO_4$). Any remaining *m*-chloroperbenzoic acid was precipitated using $Ca(OH)_2$ (0.2g) and the precipitate removed by filtration. The filtrate was concentrated under vacuum to yield a yellow oil which was purified by flash column chromatography on neutral silica using CH_2Cl_2 as eluent. The product **(88a)**, was obtained (1.703g, 7.671 x 10^{-3}mol, 67%) as a colourless oil.

Observed mass 308.1808. Calc. mass for $C_{17}H_{28}SiO_3$ 308.1808. δ_H ppm: 0.20(6H,s, H-12 and H-13) , 0.98 (9H,s, H-15, H-16 and H-17), 1.04 (3H, s, H-10) , 1.26 (3H , s, H-11), 1.55 (1H, s, O*H*), 3.16 (1H, d, J=4.4Hz, H-8), 4.11 (1H, d, J=4.3Hz, H-7), 6.76 (1H, d, J=7.3Hz, H-4or 6), 6.86 (1H, s, H-2), 6.96 (1H, d, J= 7.6Hz, H-4 or 6), 7.20 (1H, t, J=7.8Hz, H-5). δ_c, ppm, -4.44 (C-12,13), 18.16 (C-14), 25.65(C-15,16,17), 25.84 (C-10) ,28.15 (C-11) , 57.49(C-8), 64.91(C-7), 69.56(C-9), 117.93(C-2), 119.09(C-6), 119.37(C-4), 129.44(C-5), 136.76(C-3), 155.69(C-1).*m/z* (EI), 308 (7), 291 (8), 237 (53), 193 (47), 179 (43), 151,(90).ν_{max}(cm^{-1}) 3446 (O-H), 3021,2861 (C-H). λ_{max}(CH_2Cl_2) 242.8nm (ε=1106), 273.5nm (ε=1781)

6.32 cis-4-(3'-hydroxyphenyl)-2 methyl-3,4-oxiranyl-butan-2-ol (91a)

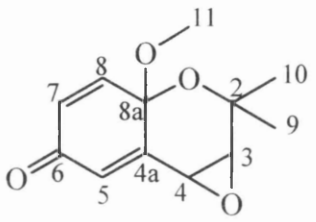


To a round bottomed flask (100ml) containing a magnetic follower was added **(88a)** (0.321g, 1.042 x 10^{-3} mol) and CsF (0.159g,1.042 x 10^{-3} mol), in methanol (50ml). The reaction mixture was stirred for 8 hours , concentrated under vacuum, dissolved in CH_2Cl_2 (50ml),washed with water (2 x 50 ml), dried over $MgSO_4$ and concentrated under vacuum to yield a yellow oil. The product was purified by flash column chromatography on neutral silica, using gradient elution with CH_2Cl_2 and EtOAc. The product **(91a)** (0.180g, 0.928 x 10^{-3} mol, 88%) was obtained as a pale yellow oil.

Observed mass 194.0943. Calc. mass for $C_{12}H_{14}O_3$ 194.0943. δ_H ppm 1.10(3H, s, H-10), 1.29 (3H, s, H-11) , 2.02 (1H, s , O**H**), 3.17(1H, d ,J= 4.4Hz ,H-8), 4.14 (1H, d, J=4.4Hz, H-7), 6.69 (1H, d, J=8.2Hz, H-4 or 6) , 6.88 (1H, d, J=7.5Hz, H-4 or 6), 6.92 (1H, s, H-2'), 6.96(1H, s, PhO**H**), 7.18 (1H, t, J=7.8Hz, H-5). δ_C ppm 25.73 (C-10), 28.18 (C-11), 57.78 (C-8), 64.89 (C-7), 70.06 (C-9), 113.21 (C-6), 114.94 (C-4), 117.91 (C-2), 129.78 (C-5), 136.55 (C-3), 156.27 (C-1). *m/z* (EI) 177 (100) , 161 (10), 137 (70), 123 (10), 107(15). ν_{max}(cm^{-1}) 3413 (O-H), 3058, 2984

(C-H). λ_{max}(MeOH) 223.2 (ε= 922), 276.9 (ε= 761)

6.33 **rel(3R,4R,8aS)-8a-methoxy-2,2-dimethyl-3,4-oxiranyl-6H-chroman-6-one (92a) and rel(3S,4S,8aS)-8a-methoxy-2,2-dimethyl-3,4-oxiranyl-6H-chroman-6-one (92b)**



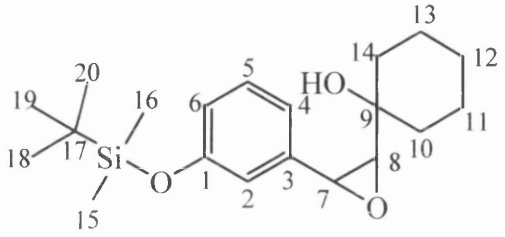
To a dry round bottomed flask (50ml) under nitrogen, fitted with a septum and a magnetic follower was added **(91a)** (0.203g,1.046 x 10^{-3}mol) in dry methanol (10ml) and PIDA (0.674g,2.093 x 10^{-3}mol) in dry methanol (5ml) with good stirring. The solution was stirred for 45 mins before addition of anhyd. K_2CO_3 (0.2g) to remove acetic acid. The reaction mixture was filtered, then concentrated under vacuum, and the products immediately separated by flash column chromatography on neutral silica using CH_2Cl_2 as eluent giving **(92a)** (0.086g, 3.87 x 10^{-4} mol, 37%) as a yellow oil.

Observed mass was 222.2400 . Calc.mass for $C_{12}H_{14}O_4$ is 222.2400

δ_H ppm: 1.15 (3H, s, H-9), 1.41 (3H,s, H-10), 2.97 (3H, s, H-11), 3.28 (1H, d, J=4.4Hz, H-3), 3.63 (1H, d, J=4.4Hz), 6.01 (1H, dd, J=2.0Hz, J=10.1Hz, H-7), 6.26 (1H, d, J=2.0Hz, H-5), 6.39 (1H, d, J=10.1Hz, H-8). δ_C ppm: 26.61 (C-9), 28.11 (C-10), 51.05 (C-11), 53.02 (C-3), 61.41 (C-4), 73.83 (C-2), 92.12 (C-8a), 127.77 (C-5), 128.16 (C-7), 144.91 (C-8), 147.96 (C-4a), 184.83 (C-6). *m/z* (EI) 191 (100), 163 (12), 149 (32) , 134 (40), 121 (20), 107 (20)ν_{max} cm^{-1} 2981,2934 (C-H), 1670 (C=O). λ_{max} ($CHCl_3$) 230.4nm (ε= 327), 244.5nm (ε= 858).A minor product **(92b)** (0.024g, 1.08 x 10^{-4} mol, 10%) was also obtained as a yellow oil. δ_H ppm: 1.37 (3H, s, H-9), 1.59 (3H, s, H-10), 3.22 (3H, s, H-11), 3.28 (1H, d, J=3.8Hz,H-3), 3.85 (1H, d, J=3.8Hz, H-4), 6.22 (1H, dd, J=2.0Hz, J=10.3Hz, H-7), 6.46 (1H, d, J=2.0Hz, H-

5), 6.68 (1H, d, J=10.3Hz), H-8). δ_C ppm: 27.11 (C-9), 27.43 (C-10), 49.6 (C-11), 51.01 (C-3), 55.98 (C-4), 90.62 (C-8a), 129.11 (C-5), 130.08 (C-7), 143.66 (C-8), 145.67 (C-4a), 185.16 (C-6).

6.34 cis-3-(3'-tert-butyldimethylsilyloxyphenyl)-1-spirocyclohexyl-2,3-oxiranylpropan-2-ol (88b)

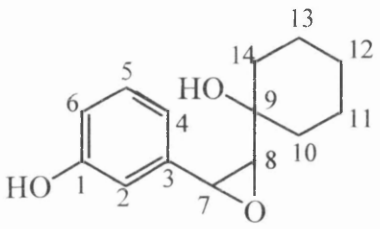


A dry round bottomed flask (50ml) was charged with a magnetic follower , fitted with a septum and flushed three times with nitrogen. **(76b)** (0.501g,1.509 x 10^{-3} mol) in dry CH_2Cl_2 (20ml) was added by syringe and kept at 0°C. To this solution was added a solution of *m*-chloroperbenzoic acid (0.302g,1.886 x 10^{-3} mol) in dry CH_2Cl_2 (5ml) at 0°C *via* a double ended needle. The reaction mixture was stirred under nitrogen at 0°C for 4 hours.The precipitated *m*-chlorobenzoic acid was removed by filtration, the precipitate washed with CH_2Cl_2 (2 x 10ml) and the combined filtrates dried ($MgSO_4$). Any remaining *m*-chloroperbenzoic acid was precipitated using Na_2CO_3 (0.2g) and the precipitate removed by filtration. The filtrate was concentrated under vacuum to yield a yellow oil which was purified by flash column chromatography on neutral silica using CH_2Cl_2 as eluent. The product **(88b)** , was obtained (0.309g,0.888 x 10^{-3}mol, 59%) as a pale yellow oil.

Observed mass was 348.2121. Calc. mass of $C_{20}H_{32}SiO_3$ is 348.2121. δ_H, 0.19(6H,s, H-15,16) , 0.98 (9H,s, H-18,19,20), 1.34,1.47,1.56,1.67 (10H, complex, m, H-10,11,12,13,14), 3.11 (1H, d, J=4.4Hz, H-8), 4.09 (1H, d, J=4.4Hz, H-7), 6.74 (1H, dd ,

J=2.4Hz, J=8.0Hz, H- 4or 6), 6.87 (1H, d,J=2.4Hz, H-2), 7.00 (1H, d, J= 7.6Hz, H-4 or 6), 7.21 (1H, t, J=7.8Hz, H-5'). δ_c, ppm, -4.41 (C-15 and C-16), 18.20 (C-17), 25.65(C-18,19,20), 21.07,21.13, 25.54, 34.02, 36.73 (C-10,11,12,13,14), 57.26(C-8), 64.73(C-7), 69.91(C-9), 117.90(C-2), 119.02(C-6), 119.3(C-4), 129.50(C-5), 137.20(C-3), 155.70(C-1).*m/z* (CI), 366(10), 331(10), 268(20), 251(100), 116(35). $\nu_{max}(cm^{-1})$ 3560, 3440(O-H), 2900, 2840 (C-H). $\lambda_{max}(CH_2Cl_3)$ 240.4nm (ε=491), 273.5nm (ε=1234)

6.35 cis-3-(3'- hydroxyphenyl)-1-spirocyclohexyl-2,3-oxiranylpropan-1-ol (91b)

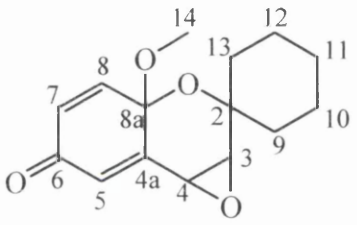


To a round bottomed flask (50ml) containing a magnetic follower was added **(88b)** (1.411g, 4.243 x 10^{-3} mol) and CsF (0.645g, 4.243 x 10^{-3} mol), in methanol (25ml). The reaction mixture was stirred for 8 hours , concentrated under vacuum, dissolved in CH_2Cl_2 (50ml),washed with water (2 x 50 ml), dried over $MgSO_4$ and concentrated under vacuum to yield a yellow oil. The product was purified by flash column chromatography on neutral silica, using gradient elution with CH_2Cl_2 and EtOAc. The product **(91b)** (0.943g,4.031 x 10^{-3} mol, 95%) was obtained as a pale yellow oil.

Observed mass for M+ NH_4^+ was 252.1600. Calc. mass for $C_{14}H_{22}O_3N$ is 252.1600. δ_H ppm 1.25,1.49,1.77 (10H, complex,m, H-10,11,12,13,14), 3.12(1H, d ,J= 4.4Hz,H-8), 4.12 (1H, d, J=4.4Hz, H-9), 6.13(1H, s, PhO**H**), 6.70 (1H, d, J=8.1Hz, H-4 or 6) , 6.92 (1H, d, J=7.6Hz, H-4 or 6), 6.96 (1H, d,J=1.4Hz, H-2), 7.19 (1H, t, J=7.9Hz, H-5). δ_C ppm

21.07,21.14,25.49,33.91,36.74 (C-10,11,12,13,14) , 57.33 (C-8), 64.62 (C-7), 70.39 (C-9), 113.08 (C-6), 114.82 (C-'), 118.00 (C-'), 129.83 (C-5), 137.15 (C-1), 156.19 (C-3). *m/z* (CI) 252 (20) , 234 (5), 217 (55), 201 (10), 154(14), 137(50), 116(100). $\nu_{max}(cm^{-1})$ 3365 (O-H), 3016, 2935, 2839 (C-H). $\lambda_{max}(CHCl_3)$ 239.8 (ε= 126), 275.5 (ε= 345), 282.1 (ε= 318)

6.36 rel(3R, 4R, 8aS)-8a-methoxy-2- spirocyclohexyl-3,4-oxiranyl-6H-chroman-6-one (99a) and rel(3S, 4S, 8aS)-8a-methoxy-2-spirocyclohexyl-3,4-oxiranyl-6H-chroman-6-one (99b)

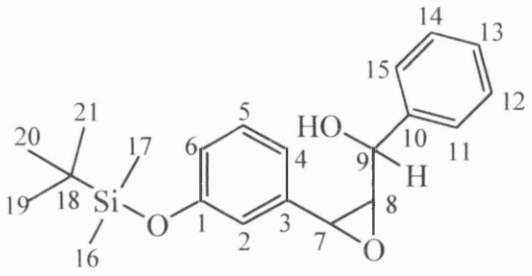


To a dry round bottomed flask (50ml),fitted with a septum and containing a magnetic follower was added under nitrogen **(91b)** (0.760g, 3.248 x 10^{-3}mol) in dry methanol (20ml) and PIDA (2.092g, 6.496 x 10^{-3}mol) in dry methanol (10ml) with good stirring. The solution was stirred for 1 hour before addition of anhyd. K_2CO_3 (0.4g) to remove acetic acid. The reaction mixture was filtered, then concentrated under vacuum, and the products immediately separated by flash column chromatography on neutral silica using CH_2Cl_2 as eluent giving **(99a)** (0.422g, 1.611 x 10^{-3} mol, 50%) as a yellow oil.

Observed mass for $M+H^+$ was 263.1283. Calc. mass for $C_{15}H_{19}O_4$ is 263.1283. δ_H ppm : 1.44-2.13 (10H, m, complex, H-9-13), 3.18 (3H, s, H-14), 3.38 (1H, d, J=3.9Hz, H-3), 3.83 (1H, d, J=3.9Hz, H-4), 6.22 (1H, dd, J=2.0Hz, J=10.3Hz, H-7), 6.46 (1H, d, J=2.0Hz, H-5), 6.68 (1H, J=10.3Hz, H-8). δ_C ppm: 21.61 (C-10), 21.86 (C-12), 25.53 (C-11), 35.33 (C-9),

36.26 (C-13), 51.01 (C-14), 52.88 (C-3), 60.68 (C-4), 74.00 (C-2), 90.01 (C-8a), 127.47 (C-5), 127.87 (C-7), 145.02 (C-8), 148.63 (C-4a), 184.88 (C-6). *m/z* (CI) 263 (8), 231 (100), 215 (20), 189 (4). $\nu_{max}(cm^{-1})$ 2937,2860,2829 (C-H) , 1676 (C=O). $\lambda_{max}(CHCl_3)$ 222.1nm (ε= 754), 259.4 (ε=2638). A minor product **(99b)** (0.129g, 4.930 x 10^{-4}mol, 15%) was also obtained as a yellow oil. δ_H ppm: 1.54-2.04 (10H, m, complex, H-9-13), 3.16 (3H, s, H-14), 3.54 (1H, d, J=4.4Hz, H-3), 3.83 (1H, d, J=4.4Hz, H-4), 6.19 (1H, dd, J=2.0Hz, J=10.2Hz, H-7), 6.45 (1H, d, J=2.0Hz, H-5), 6.64 (1H, d, J=10.2Hz, H-8). δ_C ppm: 21.61 (C-10), 22.22 (C-12), 25.51 (C-11), 35.38 (C-9), 36.27 (C-13), 49.38 (C-14), 51.07 (C-3), 54.72 (C-4), 73.81 (C-2), 120.08 (C-5), 129.82 (C-7), 143.55 (C-8), 145.90 (C-4a), 185.36 (C-6).

6.37 cis-4-(3'-tert-butyldimethylsilyloxyphenyl)-1-phenyl-3,4-oxiranylpropan-1-ol (88c)

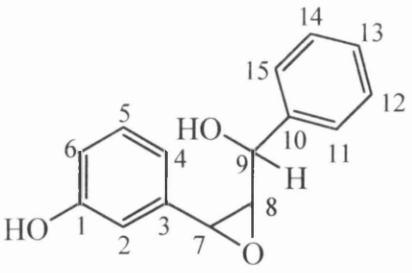


A dry round bottomed flask (50ml) was charged with a magnetic follower, fitted with a septum and flushed three times with nitrogen. **(76c)** (1.601g, 4.709 x 10^{-3} mol) in dry CH_2Cl_2 (15ml) was added by syringe and kept at 0°C. A solution of *m*-chloroperbenzoic acid (1.014g, 5.886 x 10^{-3} mol) in dry CH_2Cl_2 (10ml) was added at 0°C *via* a double ended needle and the reaction mixture stirred under nitrogen at 0°C for 2 hours.The precipitated *m*-chlorobenzoic acid was removed by filtration, the precipitate washed with CH_2Cl_2 (2 x 10ml) and the combined filtrates dried ($MgSO_4$). Any remaining *m*- chloroperbenzoic acid was

precipitated using Na_2CO_3 (0.2g) and the precipitate was removed by filtration. The filtrate was concentrated under vacuum to yield a yellow oil which was purified by flash column chromatography on neutral silica using CH_2Cl_2 as eluent. The product **(88c)**, was obtained (0.957gg, 2.688 x 10^{-3}mol, 57.1 %) as a colourless oil.

Observed mass for $M+NH_4^+$ was 374.2151. Calc. mass for $C_{21}H_{32}SiNO_3$ is 374.2151. δ_H ppm: 0.20(6H,s, Si(H-16 and H-17) , 0.99 (9H,s, H-19,20 and 21), 3.39 (1H, dd, J=4.3Hz, J=8.6Hz, H-8), 4.16 (1H, d, J=4.3Hz, H-7), 4.30 (1H, d , J= 8.6 Hz, H-9), 6.81 (1H, dd, J=2.3Hz, J=8.0Hz, H- 4or 6), 6.84(1H, s, H-2), 6.94 (1H, d, J= 7.6Hz, H- 4 or 6),7.00 (1H, t, J=7.8Hz, H-5) 7.22-7.26 (5H, complex,m, H-11-15) . δ_c, ppm, -4.38 (C-16 and C-17), 18.21 (C-18), 25.66(C-19,20,21) , 57.96(C-8), 63.27(C-7), 71.61(C-9), 118.06(C-2), 119.37(C-6), 119.92(C-4), 125.91(C-11), 128.07 (C-15) , 128.29 (C-12), 128.44 (C-14), 129.44(C-5),129.80 (C-13), 136.28(C-3), 139.22 (C-10) 155.78(C-1).*m/z* (EI) 339 (8), 327 (13), 281 (42), 251 (31), 221 (100). ν_{max}(cm^{-1}) 3420 (OH), 3066, 3032, 2956, 2932 (C-H) λ_{max}(MeOH) 217.8nm (ε= 7108), 279.1nm (ε= 1230)

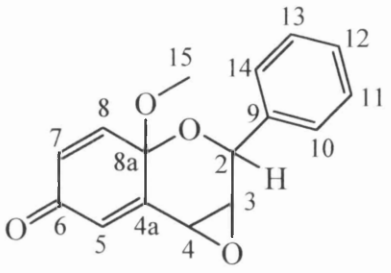
6.38 cis-3-(3'-hydroxyphenyl)-1-phenyl-2,3-oxiranylpropan-1-ol (91c)



To a round bottomed flask (100ml) containing a magnetic follower was added **(88c)** (0.897g, 2.52 x 10^{-3} mol) and CsF (0.382g, 2.52 x 10^{-3} mol) in methanol (50ml). The

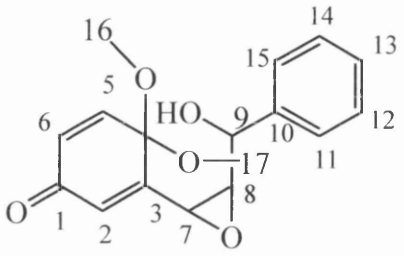
reaction mixture was stirred for 10 hours , concentrated under vacuum, dissolved in CH_2Cl_2 (50ml),washed with water (2 x 50 ml), dried over $MgSO_4$ and concentrated under vacuum to yield a yellow oil.The product was purified by flash column chromatography on neutral silica, using gradient elution with CH_2Cl_2 and EtOAc. The product **(91c)** (0.601g, 2.481 x 10^{-3} mol, 98.6%) was obtained as a pale yellow oil. Observed mass for M+H-H_2O was 225.0916. Calc. mass for $C_{15}H_{13}O_2$ 225.0916. δ_H ppm 2.91(1H, s ,O**H**), 3.40(1H, dd , J= 8.7Hz, J=4.1Hz, H-8), 4.03 (1H, s PhO**H**), 4.12 (1H, d, J=4.3Hz, H-7), 4.39 (1H, d, J=8.7Hz, H-9), 6.70 (1H, d, J=7.6Hz, H-4 or 6) , 6.82 (1H, dd, J=2.4Hz, J=8.1Hz, H-4 or 6), 6.92 –6.95 (3H, m, H-2, H-5 and 1 from H-11-15), 7.18 (4H,complex, m, from H-11-15).δ_C ppm 58.10 (C-8), 63.33 (C-7), 71.57 (C-9), 112.90 (C-6), 115.41 (C-4), 118.78 (C-2), 125.94(C-15), 128.16(C-11), 128.47(C-14), 128.49 (C-12)129.77 (C-5), 135.98 (C-3),138.95 (C-13),144.91 (C-10), 156.16 (C-1). *m/z* (CI) 260 (4), 251 (12), 225 (70), 209 (40), 154 (23). $\nu_{max}(cm^{-1})$ 3376 (O-H), 3066,3032,2930 (O-H)λ_{max} (MeOH) 220.1 nm (ε= 2653), 277.9 nm (ε= 1693)

6.39 rel(2R, 3S,4S,8aS)-8a-methoxy-2 phenyl-3,4-oxiranyl-6H-chroman-6-one (100a), rel(2R,3S,4S,8aR)-8a-methoxy-2-phenyl-3,4-oxiranyl-6H-chroman-6-one (100b) and cis-3-(6',6'-dimethoxy-3'-oxocyclohexa-1',4'-dienyl)-1-phenyl-2,3-oxiranyl propan-1-ol (102)



To a dry round bottomed flask (100ml), fitted with a septum and a magnetic follower was added under nitrogen **(91c)** (0.551g, 2.274 x 10^{-3}mol) in dry methanol (15ml) and PIDA (1.465g, 4.548 x 10^{-3}mol) in dry methanol (10ml) with good stirring. The solution was stirred for 45 mins before addition of anhyd. K_2CO_3 (0.5g) to remove acetic acid. The reaction mixture was filtered, then concentrated under vacuum, and the products immediately separated by flash column chromatography on neutral silica using CH_2Cl_2 as eluent to give isomers **(100a)** and **(100b)** (0.161g, 5.763 x 10^{-4}mol, 26.2%). Hplc showed a 3:2 ratio of isomers present. Further column chromatography on neutral silica of the mixed isomers using CH_2Cl_2 gave **(102)** (0.081g, 3.00 x 10^{-4} mol,13.2 %).

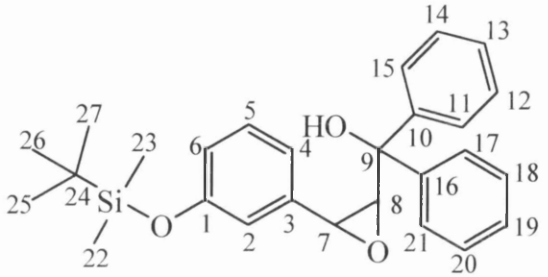
Observed mass for M+H-MeOH IS 239.0708. Calculated mass for $C_{15}H_{11}O_3$ was 239.070. δ_H ppm: 3.36 (3H, s, H-15), 3.59 (1H, d, J=3.8Hz, H-3), 3.84 (1H, d, J=3.8Hz, H-4), 6.28 (1H, dd, J=2.0Hz, J=10.3Hz, H-7), 6.49 (1H, d, J=2.0Hz, H-5), 6.78 (1H,d, J=10.3Hz, H-8). δ_C ppm: 49.74 (C-15), 51.01 (C-3), 53.03 (C-4), 69.77 (C-2), 90.67 (C-8a), 127.67 (C-11 and 13), 128.14 (C-10 and 14), 128.62 (C-12), 130.47 (C-5), 130.71 (C-7), 136.77 (C-9), 142.90 (C-8), 145.71 (C-4a), 184.66 (C-6). *m/z* (CI) 271 (5), 239 (100), 223 (7), 211 (10), 139 (20). ν_{max} (cm^{-1}) 3008,2938 (C-H), 1679 (C=O). λ_{max} (MeOH) 254.0 nm (ε= 3308) 278.7nm (ε= 1777). The minor isomer **(100b)** was obtained in a 3:1 ratio (by ^{1}H nmr) with the major isomer(0.059g). δ_H ppm: 3.10 (3H, s, H-15), 3.89 (1H, dd, J=2.4Hz, J=4.4Hz, H-3), 3.93 (1H, d, J=4.4Hz, H-4), 5.22 (1H, d, J=2.4Hz, H-2), 6.22 (1H, dd, J=2.0Hz, J=10.2Hz, H-7), 6.51 (1H, d, J=2.0Hz, H-5), 6.66 (1H, d, J=10.2Hz, H-8), 7.34-7.66 (5H, m, complex, H-10-14). δ_C ppm: 51.42 (C-15), 52.44 (C-3), 57.2 (C-4), 73.55 (C-2), 92.51 (C-8a), 127.87 (C-11 and 13), 128.14 (C-10 and 14), 128.37 (C-5), 128.52 (C-7), 128.63 (C-12), 138.21 (C-9), 144.66 (C-8), 147.84 (C-4a), 184.63 (C-6)



Further elution of the initial column gave an additional product **(102)** (0.181g, 5.793 x 10^{-4} mol, 26.4%) as a yellow oil.

Observed mass for $M+NH_4^+$ was 320.1498. Calculated mass for $C_{17}H_{22}O_5N$ is 320.1498. δ_H ppm 3.01(1H, s, O**H**), 3.19 (3H, s, H-17), 3.23 (3H, s, H-16), 3.56 (1H, dd, J=4.5Hz, J= 8.5Hz, H-8), 3.98 (1H, d, J= 4.5Hz, H-7), 4.36 (1H, d, J=8.5Hz ,H-9), 6.40 (1H,d, J= 10.0Hz, H-5), 6.43 (1H, s, H-2), 6.89 (1H, d, J= 10.0Hz, H-6), 7.25-7.38 (5H, complex, H-11-15). δ_C ppm 50.32 (C-17), 51.43 (C-16), 55.18 (C-8),60.42(C-7), 70.16 (C-9), 94.24 (C-6), 126.77 (C-11 and 15), (127.06 (C-12 and 14), 128.06 (C-4), 128.16 (C-13), 131.55 (C-5), 139.34 (C-10), 142.09 (C-2), 152.19 (C-3), 184.32 (C-1) *m/z* (CI) 271 (54), 255 (20), 239 (100), 225 (10), 184 (53), 167 (55) ν_{max} (cm^{-1}) 3452 (OH), 3063,3011,2943 (C-H), 1677 (C=O) λ_{max} (MeOH) 208.5 (ε= 4543), 228.4 (ε= 3006), 275.0 (ε=926)

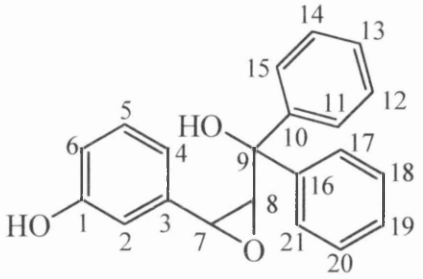
6.40 cis-3-(3'-tert-butyldimethylsilyloxyphenyl)-1,1-diphenyl-2,3-oxiranylpropan-1-ol (88d)



A dry round bottomed flask (50ml) was charged with a magnetic follower , fitted with a septum and flushed three times with nitrogen. **(76d)** (0.724g, 1.729 x 10^{-3} mol) in dry CH_2Cl_2 (20ml) was added by syringe and kept at 0°C. A solution of *m*-chloroperbenzoic acid (0.298g,1.729 x 10^{-3} mol) in dry CH_2Cl_2 (5ml) was added at 0°C *via* a double ended needle and the reaction mixture was stirred under nitrogen at 0°C for 4 hours. The precipitated *m*-chlorobenzoic acid was removed by filtration, the precipitate washed with CH_2Cl_2 (2 x 10ml) and the combined filtrates dried ($MgSO_4$). Any remaining *m*-chloroperbenzoic acid was precipitated using Na_2CO_3 (0.2g) and the precipitate removed by filtration. The filtrate was concentrated under vacuum to yield a yellow oil which was purified by flash column chromatography on neutral silica using CH_2Cl_2 as eluent. The product **(88d)** , was obtained (0.362g,8.367 x 10^{-4} mol,49 %) as a yellow oil.

Observed mass $M+NH_4^+$ was 450.2464. Calc. mass for $C_{27}H_{32}SiNO_3$ is 450.2464. δ_H, 0.17(6H,s, H-22 and H-23) , 0.97 (9H,s, H-19,20 and 21), 3.05 (1H,s,O**H**), 3.74 (1H, d, J=2.2Hz, H-8), 4.06 (1H, d, J=2.2Hz, H-7), 6.74 (1H, d , J=1.5Hz, H-2), 6.76(1H ,complex,m, H-4 or 6), 6.85 (1H, d, J= 7.7Hz, H-4 or 6), 7.14 (1H, t, J=7.7Hz, H-5), 7.15-7.79 (10H, complex, m, H10-15 and H17-21). δ_c, ppm, -4.43 (C-22 and C-23), 18.14 (C-18), 25.64(C-19,20 and 21), 53.38(C-8), 67.18(C-7), 75.57(C-9), 117.32(C-2), 118.58(C-6), 119.85(C-4), 126.39 (C-11,15,17 and 21), 127.45(C-12,14,17 and 20), 130.02(C-5) , 132.35(C-13 and C-19), 137.51(C-1), 143.10 (C-16),144.98 (C-10), 155.84(C-3).*m/z* (CI) 450 (2), 268 (10), 251 (17), 183 (100), 105 (9) . ν_{max}(cm^{-1}) 3457(O-H), 3064,3019,2958,2932 (C-H). λ_{max}($CHCl_3$) 231.2nm (ε=2091), 253.9nm (ε=4326)

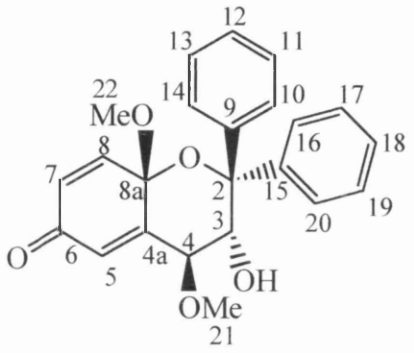
6.41 cis-3-(3'-hydroxyphenyl)-1,1-diphenyl-2,3-oxiranylpropan-1-ol (91d)



To a round bottomed flask (50ml) containing a magnetic follower was added **(88d)** (0,351g 9.27 x 10^{-4} mol) and CsF (0.141g, 9.27 x 10^{-4} mol), in methanol (25ml). The reaction mixture was stirred for 8 hours , concentrated under vacuum, dissolved in CH_2Cl_2 (50ml), washed with water (2 x 25 ml), dried over $MgSO_4$ and concentrated under vacuum to yield a yellow oil. The product was purified by flash column chromatography on neutral silica, using gradient elution with CH_2Cl_2 and EtOAc. The product **(91d)** (0.191g, 5.99 x 10^{-4} mol, 75%) was obtained as a pale yellow oil.

Observed mass of $M+NH_4^+$ was 336.1600. Calc. mass for $C_{21}H_{22}O_3N$ is 336.1600. δ_H ppm 2.90 (1H, s ,O**H**), 3.78 (1H, d ,J= 2.1Hz,H-8), 4.10 (1H, d, J=2.1Hz, H-7), 5.20(1H, s, PhO**H**), 6.72 - 6.75 (2H, m, H-2 and H-4 or H-6), 6.85 (1H, d, J=7.7Hz, H-4 or H-6), 7.17 (1H, t, J=7.1Hz, H-5), 7.20-7.52 (10H,complex,m, H-11-15 and H-17-21). δ_C ppm 55.46 (C-8), 67.21 (C-7), 75.65 (C-9), 112.41 (C-6), 115.38 (C-4), 118.28 (C-15,17), 126.34(C-11,21), 126.77(C-14,18), 127.95(C-12 ,19), 128.33(Ph), 128.36(C-19), 128.50(C-13), 129.86 (C-5), 138.30 (C-1),142.91 (C-16),144.91 (C-10), 155.86 (C-3). *m/z* (CI) 336 (4) , 318 (4), 301 (15), 200 (30), 183(100). $\nu_{max}(cm^{-1})$ 3436 (O-H), 3020, (C-H). $\lambda_{max}(CHCl_3)$ 239.3 (ε= 1004), 276.1 (ε= 1808).

6.42 rel(3R,4S,8aS)-8a-methoxy-2,2-diphenyl-3-hydroxy-4-methoxy-6H chroman-6-one (101)



To a dry round bottomed flask (50ml) fitted with a septum and a magnetic follower was added under nitrogen **(91d)** (0.170g, 5.399 x 10^{-4}mol) in dry methanol (10ml) and PIDA (0.344g, 1.068 x 10^{-3}mol) in dry methanol (5ml) with good stirring. The solution was stirred for 45 mins before addition of anhyd. K_2CO_3 (0.15g) to remove acetic acid. The reaction mixture was filtered, then concentrated under vacuum, and the products immediately separated by flash column chromatography on neutral silica using CH_2Cl_2 as eluent. The product **(101)** (0.122g , 3.364 x 10^{-3} mol, 60%) was obtained as an oil.

Observed mass for M-OMe was 347.1283 . Calculated mass for $C_{22}H_{19}O_4$ is 347.1283 . δ_H ppm: 2.64 (3H, s, H-21), 2.76 (1H, s, broad, O**H**) 3.27 (3H, s, H-22), 3.60 (1H,d, J=2.0Hz,H-3), 4.06 (1H, d, J=2.0Hz, H-4), 6.34 (1H, dd, J=2.1Hz, J=10.2Hz,H-7), 6.66 (1H, d, J=2.1Hz, H-5), 6.67 (1H, d, J=10.2Hz, H-8), 7.24-7.52 (10H, m,complex, H-10-14 and H-16-20). δ_C ppm: 50.55 (C-2), 50.61 (C-21), 51.38 (C-22), 67.82 (C-4), 75.70 (C-2), 95.06 (C-8a), 125.61, 126.60, 126.77, 127.31, 127.69, 132.13 (C-10-14 and C16-20), 142.44 (C-9), 143.37 (C-15),128.41 (C-7), 128.62 (C-5), 144.5 (C-8a), 154.63 (C-4a), 184.6 (C-6). *m/z* (EI) 347 (22), 196 (22), 183 (100), 164 (36), 77 (36).ν_{max} cm^{-1} 3464 (OH), 3061,3032,

3004,2943 (C-H), 1679 (C=O). λ_{max} (MeOH) 217.6nm (ε= 6842), 254.0 nm (ε= 2705), 277.8 nm (ε= 1876).

Chapter 7

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